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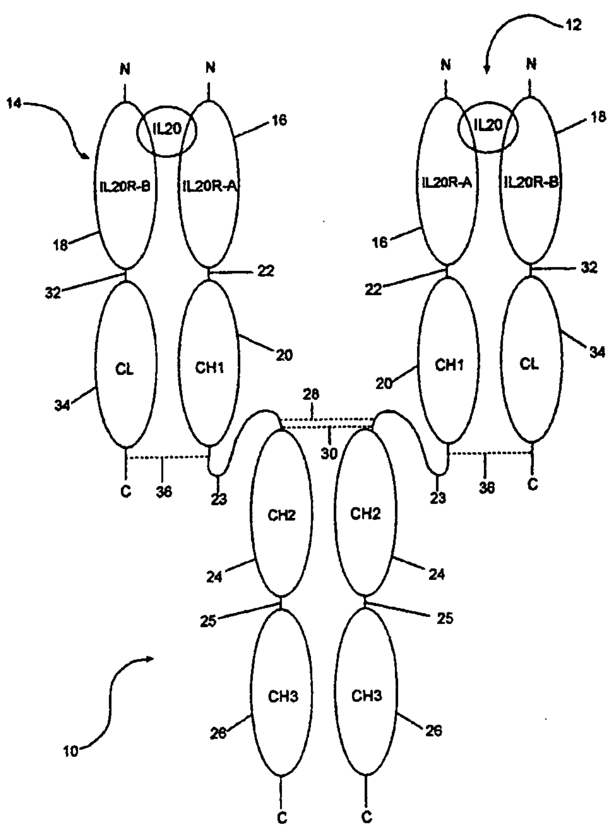
(54) Title: METHOD FOR TREATING INFLAMMATION



(57) Abstract: A method for treating IL-20 induced inflammation. An antagonist to IL-20 is administered to treat inflammation and associated diseases. The antagonist can be an antibody that binds to IL-20 or its receptor or a soluble receptor that binds to IL-20. Examples of such diseases are adult respiratory disease, psoriasis, eczema, contact dermatitis, atopic dermatitis, septic shock, multiple organ failure, inflammatory lung injury, bacterial pneumonia, inflammatory bowel disease, rheumatoid arthritis, asthma, ulcerative colitis and Crohn's disease.

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METHOD FOR TREATING INFLAMMATION

BACKGROUND OF THE INVENTION

The teachings of all of the references cited herein are incorporated in their entirety herein by reference.

Inflammation normally is a localized, protective response to trauma or microbial invasion that destroys, dilutes, or walls-off the injurious agent and the injured tissue. It is characterized in the acute form by the classic signs of pain, heat, redness, swelling, and loss of function. Microscopically, it involves a complex series of events, including dilation of arterioles, capillaries, and venules, with increased permeability and blood flow, exudation of fluids, including plasma proteins, and leukocyte migration into the area of inflammation.

Diseases characterized by inflammation are significant causes of morbidity and mortality in humans. Commonly, inflammation occurs as a defensive response to invasion of the host by foreign, particularly microbial, material. Responses to mechanical trauma, toxins, and neoplasia also may results in inflammatory reactions. The accumulation and subsequent activation of leukocytes are central events in the pathogenesis of most forms of inflammation. Deficiencies of inflammation compromise the host. Excessive inflammation caused by abnormal recognition of host tissue as foreign or prolongation of the inflammatory process may lead to inflammatory diseases as diverse as diabetes, arteriosclerosis, cataracts, reperfusion injury, and cancer, to post-infectious syndromes such as in infectious meningitis, rheumatic fever, and to rheumatic diseases such as systemic lupus erythematosus and rheumatoid arthritis. The centrality of the inflammatory response in these varied disease processes makes its regulation a major element in the prevention control or cure of human disease.

An important cytokine in the inflammatory process is interleukin-8 (IL-8). IL-8 is a chemokine. It was identified as an agonist for neutrophils on the basis of two effects, chemotaxis and the release of granule enzymes. IL-8 binds to two receptors on neutrophils. IL-8 receptors are also found on monocytes, basophils, and eosinophils. In human fibroblasts, cytomegalovirus has been shown to induce the expression of IL-8 receptors and to replicate more rapidly when cells are exposed to IL-8. IL-8 is a potent chemoattractant for neutrophils; and the early stages of periodontal disease are characterized by the influx of neutrophils. IL-8 is a potent inducer of angiogenesis in several angiogenesis-dependent chronic inflammatory conditions, including rheumatoid arthritis, psoriasis, and idiopathic pulmonary fibrosis. Additionally, IL-8 is an important source of angiogenic activity in human lung cancer. Also, IL-8 expression correlates with experimental metastatic activity of some melanoma cell lines. Thus, an effective method to treat inflammatory diseases would be to administer an agent that would inhibit IL-8.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURES: 1-8 are schematic representations of a representative number of embodiments of the IL-20 soluble receptor.

DESCRIPTION OF THE INVENTION

The present invention fills this need by providing for a method for treating inflammation in which IL-20 plays a role, comprising administering to a mammal in need of treatment of inflammation an antagonist to IL-20 or an antagonist to the IL-20 receptor. The antagonist to IL-20 can be an antibody, antibody fragment or single-chain antibody that binds to IL-20, a soluble receptor that binds to IL-20. The antagonist to the IL-20 receptor can be an antibody, antibody fragment, single-chain antibody or small molecule that binds to the IL-20 receptor. Also an anti-sense nucleotide that binds to the mRNA that encodes IL-20 can be used as an antagonist. We have shown that IL-20 up-regulates IL-8. Inflammatory diseases in which IL-8 plays a

significant role, and for which a decrease in IL-8 would be beneficial are, adult respiratory disease (ARD), septic shock, multiple organ failure, inflammatory lung injury such as asthma or bronchitis, bacterial pneumonia, psoriasis and inflammatory bowel disease such as ulcerative colitis and Crohn's disease, eczema, atopic dermatitis and contact dermatitis. Thus, antagonists to IL-20 can be used to treat these diseases.

The teachings of all the references cited herein are incorporated in their entirety by reference.

Definitions

Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete polypeptide.

The term "complement/anti-complement pair" denotes non-identical moieties that form a non-covalently associated, stable pair under appropriate conditions. For instance, biotin and avidin (or streptavidin) are prototypical members of a complement/anti-complement pair. Other exemplary complement/anti-complement pairs include receptor/ligand pairs, antibody/antigen (or hapten or epitope) pairs, sense/antisense polynucleotide pairs, and the like. Where subsequent dissociation of the complement/anti-complement pair is desirable, the complement/anti-complement pair preferably has a binding affinity of $<10^9 M^{-1}$.

The term "complements of a polynucleotide molecule" is a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

The term "contig" denotes a polynucleotide that has a contiguous stretch of identical or complementary sequence to another polynucleotide. Contiguous sequences are said to "overlap" a given stretch of polynucleotide sequence either in their entirety or along a partial stretch of the polynucleotide. For example, representative contigs to the polynucleotide sequence 5'-ATGGCTTAGCTT-3' are 5'-TAGCTTgagtct-3' and 3'-gtcgacTACCGA-5'.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons contain different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature 316*:774-78 (1985).

An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide is substantially free of other

polypeptides, particularly other polypeptides of animal origin. It is preferred to provide the polypeptides in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

The term "operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, *e.g.*, transcription initiates in the promoter and proceeds through the coding segment to the terminator.

A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nucleotides in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10 amino acid residues are commonly referred to as "peptides".

The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate

groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

The term "receptor" denotes a cell-associated protein that binds to a bioactive molecule (i.e., a ligand) and mediates the effect of the ligand on the cell. Membrane-bound receptors are characterized by a multi-domain structure comprising an extracellular ligand-binding domain and an intracellular effector domain that is typically involved in signal transduction. Binding of ligand to receptor results in a conformational change in the receptor that causes an interaction between the effector domain and other molecule(s) in the cell. This interaction in turn leads to an alteration in the metabolism of the cell. Metabolic events that are linked to receptor-ligand interactions include gene transcription, phosphorylation, dephosphorylation, increases in cyclic AMP production, mobilization of cellular calcium, mobilization of membrane lipids, cell adhesion, hydrolysis of inositol lipids and hydrolysis of phospholipids. In general, receptors can be membrane bound, cytosolic or nuclear, monomeric (*e.g.*, thyroid stimulating hormone receptor, beta-adrenergic receptor) or multimeric (*e.g.*, PDGF receptor, growth hormone receptor, IL-3 receptor, GM-CSF receptor, G-CSF receptor, erythropoietin receptor and IL-6 receptor).

The term "secretory signal sequence" denotes a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

Molecular weights and lengths of polymers determined by imprecise analytical methods (*e.g.*, gel electrophoresis) will be understood to be approximate values. When such a value is expressed as “about” X or “approximately” X, the stated value of X will be understood to be accurate to ±10%.

Introduction

The present invention relates to the treatment of inflammation and inflammatory diseases in which IL-20 plays a role either in initiating or spreading or maintenance by administering to the afflicted individual an antagonist to IL-20. That antagonist can be an antibody to IL-20, a soluble receptor that binds to IL-20, an anti-sense molecule or an antibody that binds to either the IL-20RA subunit or the IL-20RB subunit of the IL-20 receptor.

IL-20 is defined and methods for producing it and antibodies to IL-20 are contained in International Patent Application No. PCT/US98/25228, publication no. WO 99/27103,published November 25, 1998 and U.S. Patent Application No. 09/313,458 filed May 17, 1999. The polynucleotide and polypeptide of human IL-20 are represented by SEQ ID NOs: 1 - 4, and mouse IL-20 by SEQ ID NOs: 5-9.

The receptor to IL-20 has been discovered and is a heterodimer comprised of the polypeptide termed 'IL-20RA' (formally called Zcytor7) and a polypeptide termed 'IL-20RB'. The IL-20RA polypeptide, nucleic acid that encodes it, antibodies to IL-20RA, and methods for producing it are disclosed in U.S. Patent No. 5,945,511 issued August 31, 1999. SEQ ID NOs: 10 - 12 are the IL-20RA polynucleotides and polypeptides. The extracellular domain of the human IL-20RA is comprised of a polypeptide selected from the group consisting of SEQ ID NOs: 12, 55, 63 and 65, the full-length receptor subunit being comprised of SEQ ID NO: 11. The extracellular domain of mouse IL-20RA is SEQ ID NO: 38, SEQ ID NO: 37 being the entire mouse IL-20RA.

The extracellular domain of IL-20RB (SEQ ID NOs: 13-14, and a variant SEQ ID NOs: 18 and 19) is comprised of a polypeptide selected from the group consisting of SEQ ID NOs: 15, 59, 61, 67, 68 and 69. Preferably, the extracellular domain of the IL-20RA polypeptide and the extracellular domain of the IL-20RB polypeptide are covalently linked together. In a preferred embodiment one extracellular subunit polypeptide has a constant region of a heavy chain of an immunoglobulin fused to its carboxy terminus and the other extracellular subunit has a constant light chain of an immunoglobulin (Ig) fused to its carboxy terminus such that the two polypeptides come together to form a soluble receptor and a disulfide bond is formed between the heavy and the light Ig chains. In another method, a peptide linker could be fused to the two carboxy-termini of the polypeptides to form a covalently bonded soluble receptor.

SEQ ID NOs: 22 and 23 are constructs of the extracellular domain of IL-20RA fused to a mutated human immunoglobulin gamma 1 constant region produced according to the procedure set forth in example 5. SEQ ID NO: 62 is the predicted mature sequence without the signal sequence. SEQ ID NOs: 20 and 21 are constructs of the extracellular domain of IL-20RB fused to wild type human immunoglobulin kappa light chain constant region produced according to the procedure of example 5. SEQ ID NO: 60 is the predicted mature sequence without the signal sequence. Figure 1 depicts the heterotetramer produced by example 5.

SEQ ID NOs: 52 and 53 are constructs of the extracellular domain of IL-20RA fused to a mutated human immunoglobulin gamma 1 constant region produced according to the procedure set forth in example 12. SEQ ID NO: 54 is the predicted mature sequence without the signal sequence. SEQ ID NOs: 56 and 57 are constructs of the extracellular domain of IL-20RB fused to wild type human immunoglobulin kappa light chain constant region produced according to the procedure of example 12. SEQ ID NO: 58 is the predicted mature sequence without the signal sequence. The resultant heterotetramer is almost identical to that produced by example 5, the primary difference being the absence of a polypeptide linker between the extracellular domains and the beginning of the Ig constant regions, 22 in Figure 1. Hereinafter, the term "extracellular domain of a receptor" means the extracellular domain of the receptor or a portion of the extracellular domain that is necessary for binding to its ligand, in this case the ligand being IL-20.

One can link together the extracellular domains of IL-20RA and IL-20RB in a number of ways such that the resultant soluble receptor can bind to IL-20. Figures 1-8 illustrate a representative number of embodiments of the present invention. Common elements in each of the drawings are given the same number. Figure 1 represents the embodiment of the present invention produced according to example 5 below. The soluble receptor construct, designated 10, is comprised of two IL-20 binding site polypeptide chains designated 12 and 14. Each binding site is comprised of the extracellular domain of IL-20RA, designated 16, and the extracellular domain of IL-20RB designated 18.

The extracellular domain, 16, of IL-20RA is linked to the constant heavy one (CH1) domain, 20, of the human immunoglobulin gamma 1 heavy chain constant region via linker 22, which is SEQ ID NO:72. The CH1 domain, 20, is then linked to the CH2 domain, 24, via hinge region 23. The CH2 domain, 24, is linked to the CH3 domain, 26, via hinge region 25.

Comparing the construct of Figure 1 with SEQ ID NO:22, the extracellular domain, 16, of IL-20RA extends from amino acid residues 36, a valine, to

and including amino acid residue 249, a glutamine of SEQ ID NO:22. Polypeptide linker, 22, extends from amino acid residue 250, a glycine to and including amino acid residue 264, a serine, of SEQ ID NO:22. The CH1 domain, 22 of Figure 1, extends from amino acid residue 265, an alanine, to and including amino acid residue 362, a valine, of SEQ ID NO:22. Hinge region 23 of Figure 1 extends from amino acid residue 363, a glutamic acid to and including amino acid residue 377, a proline, of SEQ ID NO: 22. Chains 12 and 14 are disulfide-bonded together by means of disulfide bonds 28 and 30. The disulfide bonds are formed between the heavy chains by the cysteine residues at positions 373 and 376 of SEQ ID NO: 22 of each of the two heavy chains.

Extracellular domain, 18, of IL-20RB is linked to the constant region of the human kappa light chain (CL), 34 of Figure 1 via polypeptide linker 32, which is the polypeptide SEQ ID NO: 72. The extracellular domain, 18, of IL-20RB extends from amino acid residue 30, a valine, to and including amino acid residue 230, an alanine, of SEQ ID NO: 20. Polypeptide linker, 32, extends from amino acid residue 231, a glycine, to and including amino acid residue 245, a serine, of SEQ ID NO:20. The kappa constant light region, 34, extends from amino acid residue 246, an arginine, to and including the final amino acid residue 352, a cysteine, of SEQ ID NO:20. The cysteine at position 352 of SEQ ID NO: 20 forms a disulfide bond, 36 in Figure 1, with the cysteine at position 367 of SEQ ID NO: 22. The constant light chain 34 is thus linked to the hinge region, 23, by disulfide bond, 36. In this way, the extracellular domain, 16, of IL-20RA is linked to the extracellular domain, 18, of IL-20RB to form a soluble receptor.

If the cysteine residues at positions 373 and 376 of SEQ ID NO:22 were changed to different amino acid residues, the two IL-20 binding polypeptides, 12 and 14, would not be disulfide bonded together and would form a construct shown in Figure 2. having hinge region, 27.

Figure 3 shows a very simple soluble receptor 38 of the present invention wherein extracellular domain, 16, of IL-20RA is connected to the extracellular domain, 18, of IL-20RB by means of a polypeptide linker, 40. The polypeptide linker extends from the amino terminus of extracellular domain, 16, of IL-20RA and is connected to the carboxyl terminus of the extracellular domain, 18, of IL-20RB. The polypeptide linker should be between 100-240 amino acids in length, preferably about 170 amino acid residues in length. A suitable linker would be comprised of glycine and serine residues. A possible linker would be multiple units of SEQ ID NO: 72, preferably about 12.

Figure 4 shows an embodiment that has the extracellular domain, 16, of IL-20RA linked to the extracellular domain, 18, of IL-20RB by means of linker 40, as in Figure 3. While the extracellular domain, 16, of IL-20RA is linked to the CH1 domain, 20, as in Figure 1 by means of polypeptide linker 42, which should be about 30 amino acid residues in length. An ideal linker would be comprised of glycine and serine as in SEQ ID NO: 72, and the hinge sequence, 23 of Figure 1.

Figure 5 shows another possible embodiment of the present invention. In this embodiment, a polypeptide linker 44 of about 15 amino acid residue, *e.g.* SEQ ID NO: 72, links the carboxyl terminus of the extracellular domain, 18, of IL-20RB with the amino terminus of the extracellular domain, 16, of IL-20RA. A polypeptide linker 46 of about 30 amino acid residues extends from the carboxy terminus of the extracellular domain, 16, of IL-20RA to the CH2 domain. The carboxyl terminus of linker 46 would preferably be comprised of the hinge region extending from amino acid residue 363, a glutamic acid to and including amino acid residue 377, a proline, of SEQ ID NO: 22. Nonetheless, polypeptide linker 46 would ideally have at least one cysteine residue at its carboxyl terminus so a disulfide bond could be formed.

The soluble IL-20 receptor of Figure 6 is identical to that of Figure 1 except for the CH3 domain, 26 of Figure 1, is not present on the embodiment of Figure 6. The CH3 region begins at amino acid residue 488, a glycine, and extends to the last residue 594 of SEQ ID NO: 22.

Figure 7 shows a soluble IL-20 receptor construct that is identical to the construct of Figure 1 except both the CH2, and CH3 domains are absent. The CH2 and CH3 domains run from amino acid residue 378, an alanine, to the end of the polypeptide sequence of SEQ ID NO: 22.

Figure 8 shows a construct wherein both IL-20RA, 16, and IL-20RB have a polypeptide linker, 48, fused to their respective carboxyl termini. Each polypeptide linker has two cysteine residues such that when they are expressed the cysteines form two disulfide bonds, 50 and 52. In this case the polypeptide linker is comprised of the hinge region, 23 in Figure 1. The hinge region is comprised of amino acid residues 363, a glutamine, to and including amino acid residue 377 of SEQ ID NO: 22.

In another aspect of the invention, a method is provided for producing a soluble receptor comprised of extracellular domains of IL-20RA and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised of a transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame the DNA that encodes the extracellular portion of IL-20RA and the DNA that encodes an immunoglobulin light chain constant

region;(b) introducing into the host cell a second DNA construct comprised of a transcriptional promoter operatively linked to a second secretory signal followed downstream by and in proper reading frame a DNA sequence that encodes the extracellular portion of IL-20RB and a DNA sequence that encodes an immunoglobulin heavy chain constant region domain selected from the group consisting of C_H1, C_H2, C_H3 and C_H4; (c) growing the host cell in an appropriate growth medium under physiological conditions to allow the secretion of a fusion protein comprised of the extracellular domain of IL-20RA and IL-20RB; and (d) isolating the polypeptide from the host cell. In one embodiment, the second DNA sequence further encodes an immunoglobulin heavy chain hinge region wherein the hinge region is joined to the heavy chain constant region domain. In another embodiment, the second DNA sequence further encodes an immunoglobulin variable region joined upstream of and in proper reading frame with the immunoglobulin heavy chain constant region.

In an alternative embodiment, a method is provided for producing a soluble receptor comprised of the extracellular domains of IL-20RA and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised of a transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame the DNA that encodes the extracellular portion of IL-20RB and the DNA that encodes an immunoglobulin light chain constant region;(b) introducing into the host cell a second DNA construct comprised of a transcriptional promoter operatively linked to a second secretory signal followed downstream by and in proper reading frame a DNA sequence that encodes the extracellular portion of IL-20RA and a DNA sequence that encodes an immunoglobulin heavy chain constant region domain selected from the group consisting of C_H1, C_H2, C_H3 and C_H4; (c) growing the host cell in an appropriate growth medium under physiological conditions to allow the secretion of a dimerized heterodimeric fusion protein comprised of the extracellular domain of IL-20RA and IL-20RB; and (d) isolating the dimerized polypeptide from the host cell. In one embodiment, the second DNA sequence further encodes an immunoglobulin heavy chain hinge region wherein the hinge region is joined to the heavy chain constant region domain. In another embodiment, the second DNA sequence further encodes an immunoglobulin variable region joined upstream of and in proper reading frame with the immunoglobulin heavy chain constant region. (See U.S. Patent No. 5,843,725.)

As used herein, the term "antibodies" includes polyclonal antibodies, affinity-purified polyclonal antibodies, monoclonal antibodies, and antigen-binding fragments, such as $F(ab')_2$ and Fab proteolytic fragments. Genetically engineered intact antibodies or fragments, such as chimeric antibodies, Fv fragments, single chain

antibodies and the like, as well as synthetic antigen-binding peptides and polypeptides, are also included. Non-human antibodies may be humanized by grafting non-human CDRs onto human framework and constant regions, or by incorporating the entire non-human variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced. The binding affinity of an antibody can be readily determined by one of ordinary skill in the art, for example, by Scatchard analysis. A variety of assays known to those skilled in the art can be utilized to detect antibodies that bind to protein or peptide. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.) (Cold Spring Harbor Laboratory Press, 1988). Representative examples of such assays include: concurrent immunoelectrophoresis, radioimmunoassay, radioimmuno-precipitation, enzyme-linked immunosorbent assay (ELISA), dot blot or Western blot assay, inhibition or competition assay, and sandwich assay.

We have shown that IL-20 up-regulates IL-8. Inflammatory diseases in which IL-8 plays a significant role, and for which a decrease in IL-8 would be beneficial are, adult respiratory disease (ARD), septic shock, multiple organ failure, inflammatory lung injury such as asthma or bronchitis, bacterial pneumonia, psoriasis and inflammatory bowel disease such as ulcerative colitis and Crohn's disease, eczema, atopic dermatitis and contact dermatitis. Thus, antagonists to IL-20 can be used to treat these diseases.

Biology of IL-20, Its receptor and Its Role in Psoriasis

Two orphan class II cytokine receptors, both of which are expressed in skin, were identified as IL-20 receptor subunits. Both IL-20 receptor subunits are required for ligand binding, distinguishing their role from that of subunits in the four other known class II cytokine receptors. IL-20RA and IL-20RB are also coexpressed in a number of human tissues besides skin, including ovary, adrenal gland, testis, salivary gland, muscle, lung, kidney, heart and to a lesser degree the small intestine suggesting additional target tissues for IL-20 action. Additionally, we have detected IL-20RA mRNA but not IL-20RB mRNA in several human tissues including stomach, thyroid, pancreas, uterus, brain and prostate suggesting that IL-20RA may partner with other class II receptor subunits. We conclude that the IL-20 heterodimeric receptor is

structurally similar to other class II cytokine receptors and is expressed in skin where we have demonstrated activity of the IL-20 ligand.

Two lines of evidence indicate that a role IL-20 and its receptor are involved in psoriasis. This multigenic skin disease is characterized by increased keratinocyte proliferation, altered keratinocyte differentiation, and infiltration of immune cells into the skin. The first line of evidence for a role of IL-20 in psoriasis is that the observed hyperkeratosis and thickened epidermis in the transgenic mice that resemble human psoriatic abnormalities. Decreased numbers of tonofilaments, thought to be related to defective keratinization, are a striking feature of human psoriasis. Intramitochondrial inclusions have been found in both chemically induced and naturally occurring hyperplastic skin conditions in mice. The cause of the inclusions and their effects on mitochondrial function, if any, are unknown. We conclude that IL-20 transgenic mice exhibit many of the characteristics observed in human psoriasis.

A second line of evidence that implicates the IL-20 receptor in psoriasis is that both IL-20RA and IL-20RB mRNA are markedly upregulated in human psoriatic skin compared to normal skin. Both IL-20 receptor subunits are expressed in keratinocytes throughout the epidermis and are also expressed in a subset of immune and endothelial cells. We propose that increased expression of an activated IL-20 receptor may alter the interactions between endothelial cells, immune cells and keratinocytes, leading to dysregulation of keratinocyte proliferation and differentiation.

A crucial step in understanding the function of a novel cytokine is the identification and characterization of its cognate receptor. We have successfully used a structure-based approach to isolate a novel interleukin that ultimately led to the isolation of its receptor. IL-20 stimulates signal transduction in the human keratinocyte HaCaT cell line, supporting a direct action of this novel ligand in skin. In addition, IL-1β, EGF and TNF-α, proteins known to be active in keratinocytes and to be involved with proliferative and pro-inflammatory signals in skin, enhance the response to IL-20. In both HaCaT and BHK cells expressing the IL-20 receptor, IL-20 signals through STAT3.

Use of Antagonist to IL-20 to Treat Psoriasis

As indicated in the discussion above and the examples below, IL-20 is involved in the pathology of psoriasis. The present invention is in particular a method for treating psoriasis by administering antagonists to IL-20. The antagonists to IL-20 can either be a soluble receptor that binds to IL-20 or antibodies, single chain antibodies

or fragments of antibodies that bind to either IL-20 or the IL-20 receptor. The antagonists will thus prevent activation of the IL-20 receptor.

Psoriasis is one of the most common dermatologic diseases, affecting up to 1 to 2 percent of the world's population. It is a chronic inflammatory skin disorder characterized by erythematous, sharply demarcated papules and rounded plaques, covered by silvery micaceous scale. The skin lesions of psoriasis are variably pruritic. Traumatized areas often develop lesions of psoriasis. Additionally, other external factors may exacerbate psoriasis including infections, stress, and medications, *e.g.* lithium, beta blockers, and anti-malarials.

The most common variety of psoriasis is called plaque type. Patients with plaque-type psoriasis will have stable, slowly growing plaques, which remain basically unchanged for long periods of time. The most common areas for plaque psoriasis to occur are the elbows knees, gluteal cleft, and the scalp. Involvement tends to be symmetrical. Inverse psoriasis affects the intertriginous regions including the axilla, groin, submammary region, and navel, and it also tends to affect the scalp, palms, and soles. The individual lesions are sharply demarcated plaques but may be moist due to their location. Plaque-type psoriasis generally develops slowly and runs an indolent course. It rarely spontaneously remits.

Eruptive psoriasis (guttate psoriasis) is most common in children and young adults. It develops acutely in individuals without psoriasis or in those with chronic plaque psoriasis. Patients present with many small erythematous, scaling papules, frequently after upper respiratory tract infection with beta-hemolytic streptococci. Patients with psoriasis may also develop pustular lesions. These may be localized to the palms and soles or may be generalized and associated with fever, malaise, diarrhea, and arthralgias..

About half of all patients with psoriasis have fingernail involvement, appearing as punctate pitting, nail thickening or subungual hyperkeratosis. About 5 to 10 percent of patients with psoriasis have associated joint complaints, and these are most often found in patients with fingernail involvement. Although some have the coincident occurrence of classic Although some have the coincident occurrence of classic rheumatoid arthritis, many have joint disease that falls into one of five type

associated with psoriasis: (1) disease limited to a single or a few small joints (70 percent of cases); (2) a seronegative rheumatoid arthritis-like disease; (3) involvement of the distal interphalangeal joints; (4) severe destructive arthritis with the development of "arthritis mutilans"; and (5) disease limited to the spine.

Psoriasis can be treated by administering antagonists to IL-20. The preferred antagonists are either a soluble receptor to IL-20 or antibodies, antibody fragments or single chain antibodies that bind to either the IL-20 receptor or to IL-20. The antagonists to IL-20 can be administered alone or in combination with other established therapies such as lubricants, keratolytics, topical corticosteroids, topical vitamin D derivatives, anthralin, systemic antimetabolites such as methotrexate, psoralen-ultraviolet-light therapy (PUVA), etretinate, isotretinoin, cyclosporine, and the topical vitamin D3 derivative calcipotriol. The antagonists, in particularly the soluble receptor or the antibodies that bind to IL-20 or the IL-20 receptor can be administered to individual subcutaneously, intravenously, or transdermally using a cream or transdermal patch that contains the antagonist of IL-20. If administered subcutaneously, the antagonist can be injected into one or more psoriatic plaques. If administered transdermally, the antagonists can be administered directly on the plaques using a cream containing the antagonist to IL-20.

Use of Antagonists to IL-20 to Treat Inflammatory Conditions of the Lung.

Antagonists to IL-20 can be administered to a person who has asthma, bronchitis or cystic fibrosis or other inflammatory lung disease to treat the disease. The antagonists can be administered by any suitable method including intravenous, subcutaneous, bronchial lavage, and the use of inhalant containing an antagonist to IL-20.

Administration of Antagonists to IL-20

The quantities of antagonists to IL-20 necessary for effective therapy will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medications administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used *in vitro* may provide useful guidance in the amounts useful for *in vivo* administration of

these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Methods for administration include oral, intravenous, peritoneal, intramuscular, transdermal or administration into the lung or trachea in spray form by means or a nebulizer or atomizer. Pharmaceutically acceptable carriers will include water, saline, buffers to name just a few. Dosage ranges would ordinarily be expected from 1μg to 1000μg per kilogram of body weight per day. A dosage for an average adult of the IL-20 soluble receptor would be about 25 mg given twice weekly as a subcutaneous injection. A dosage of an antibody that binds to IL-20 would be about 25 mg given twice weekly. A mixture of antibodies that bind to the IL-20RA and IL-20RB subunits would be about 25 mg given twice weekly for an adult. Injections could be given at the site of psoriatic lesions for the treatment of psoriasis. For subcutaneous or intravenous administration of the antagonist to IL-20, the antibody or soluble receptor can be in phosphate buffered saline. Also in skin diseases such as psoriasis, the antagonist to IL-20 can be administered via an ointment or transdermal patch. The doses by may be higher or lower as can be determined by a medical doctor with ordinary skill in the art. For a complete discussion of drug formulations and dosage ranges *see Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Co., Easton, Penn., 1996), and *Goodman and Gilman's: The Pharmacological Bases of Therapeutics*, 9th Ed. (Pergamon Press 1996).

The invention is further illustrated by the following non-limiting examples.

Example 1

Up-regulation of IL-8 by IL-20

Methods:

Normal Human Epidermal neonatal keratinocytes (NHEK) (from Clonetics) at passage 2 were plated and grown to confluency in 12 well tissue culture plates. KGM (Keratinocyte growth media) was purchased from Clonetics. When cells reached confluency, they were washed with KGM media minus growth factors = KBM (keratinocyte basal media). Cells were serum starved in KBM for 72 hours prior to the addition of test compounds. Thrombin at 1 I.U./mL and trypsin at 25nM were used as positive controls. One mL of media/well was added. KBM only was used as the negative control.

IL-20 was made up in KBM media and added at varying concentrations, from 2.5μg/ml down to 618ng/mL in a first experiment and from 2.5μg/mL down to 3ng/mL in a second experiment.

Cells were incubated at 37° C, 5% CO_2 for 48 hours. Supernatants were removed and frozen at -80° C for several days prior to assaying for IL-8 and GM-CSF levels. Human IL-8 Immunoassay kit # D8050 (RandD Systems, Inc.) and human GM-CSF Immunoassay kit # HSGMO (RandD Systems, Inc.) were used to determine cytokine production following manufacturer's instructions.

Results

The results indicated that the expression of IL-8 and GM-CSF were induced by IL-20.

Example 2

Cloning of IL-20RB

Cloning of IL-20RB coding region

Two PCR primers were designed based on the sequence from International Patent Application No. PCT/US99/03735 (publication no. WO 99/46379) filed on March 8, 1999. SEQ ID NO: 16 contains the ATG (Met1) codon with an EcoRI restriction site, SEQ ID NO: 17 contains the stop codon (TAG) with an XhoI restriction site. The PCR amplification was carried out using a human keratinocyte (HaCaT) cDNA library DNA as a template and SEQ ID NO: 16 and SEQ ID NO: 17 as primers. The PCR reaction was performed as follows: incubation at 94°C for 1 min followed by 30 cycles of 94°C for 30 sec and 68°C for 2 min, after additional 68°C for 4 min, the reaction was stored at 4°C. The PCR products were run on 1% Agarose gel, and a 1 kb DNA band was observed. The PCR products were cut from the gel and the DNA was purified using a QIAquick Gel Extraction Kit (Qiagen). The purified DNA was digested with EcoRI and XhoI, and cloned into a pZP vector that was called pZP7N. A pZP plasmid is a mammalian expression vector containing an expression cassette having the mouse metallothionein-1 promoter, human tPA leader peptide, multiple restriction sites for insertion of coding sequences, a Glu-Glu tag, and a human growth hormone terminator. The plasmid also has an E. coli origin of replication, a mammalian selectable marker expression unit having an SV40 promoter, an enhancer and an origin of replication, as well as a DHFR gene, and the SV40 terminator. Several IL-20RB-pZP7N clones were sequenced. They all contain three non-conservative mutations compared with the sequence of IL-20RB in PCT/US99/03735: (sequence IL-20RB-pZP7N), 146 Pro (CCC) -- Thr (ACC), 148 His (CAT) -- Asp (GAT), and 171 Thr (ACG) -- Arg (AGG).

To verify the three substitutions in IL-20RB-pZP7N clone, PCR amplification was carried out using three difference cDNA sources -- fetal skin marathon cDNA, HaCaT cDNA library DNA, and prostate smooth muscle cDNA library DNA -- as templates. The PCR products were gel purified and sequenced. The

sequence of each of the three PCR products was consistent with that of the IL-20RB-pZP7N clone. IL-20RB is SEQ ID NO: 13 and 14, and the mature extracellular domain is SEQ ID NO: 15.

Example 3

Binding of IL-20 to IL-20RB/ IL-20RA Heterodimer

A cell-based binding assay was used to verify IL-20 binds to IL-20RA-IL-20RB heterodimer.

Expression vectors containing known and orphan Class II cytokine receptors (including IL-20RA and IL-20RB) were transiently transfected into COS cells in various combinations, which were then assayed for their ability to bind biotin-labeled IL-20 protein. The results show IL-20RB- IL-20RA heterodimer is a receptor for IL-20. The procedure used is described below.

The COS cell transfection was performed in a 12-well tissue culture plate as follows: 0.5 µg DNA was mixed with medium containing 5 µl lipofectamine in 92 µl serum free Dulbecco's modified Eagle's medium (DMEM) (55 mg sodium pyruvate, 146 mg L-glutamine, 5 mg transferrin, 2.5 mg insulin, 1 µg selenium and 5 mg fetuin in 500 ml DMEM), incubated at room temperature for 30 minutes and then added to 400 µl serum free DMEM media. This 500 µl mixture was then added to 1.5 x 10^5 COS cells/well and incubated for 5 hours at 37° C. 500 µl 20% fetal bovine serum (FBS) DMEM media was added and incubated overnight.

The assay, a modification of the "secretion trap" (Davis, S., *et al., Cell 87*: 1161-1169 (1996), was performed as follows: cells were rinsed with PBS/1% bovine serum albumin (BSA) and blocked for 1 hour with TNB (0.1 M Tris-HCl, 0.15 M NaCl and 0.5% Blocking Reagent (NEN Renaissance TSA-Direct Kit Cat# NEL701) in water). This was followed by a one-hour incubation with 3 µg/ml biotinylated IL-20 protein in TNB. Cells were washed with PBS/1% BSA and incubated for another hour with 1:300 diluted streptavidin-HRP (NEN kit) in TNB. Following another wash, cells were fixed for 15 minutes with 1.8% Formaldehyde in phosphate-buffered saline (PBS).

Cells were then washed with TNT (0.1 M Tris-HCL, 0.15 M NaCl, and 0.05% Tween-20 in water). Positive binding signals were detected following a five-minute incubation with fluorescein tyramide reagent diluted 1:50 in dilution buffer (NEN kit). Cells were washed with TNT, preserved with Vectashield Mounting Media (Vector Labs) diluted 1:5 in TNT, and visualized using an FITC filter on an inverted fluorescent microscope.

Example 4

Up-regulation of Inflammatory Cytokines by IL-20

Cell Treatment

The human keratinocyte cell line, HaCaT was grown at 37°C to several days post-confluence in T-75 tissue culture flasks. At this point, normal growth media (DMEM + 10% FBS) was removed and replaced with serum-free media. Cells were then incubated for two days at 37°C. DMEM was then removed and four flasks of cells per treatment were treated with one of each of the following conditions for four hours at 37°C: recombinant human (rh) IL-1 alpha at 5 ng/mL, rh IL-1 alpha at 20 ng/mL, rh IL-1 alpha at 5 ng/mL + IL-20 at 1μg/mL, IL-20 at 1μg/mL, or rh IL-10 at 10 ng/mL.

RNA Isolation

Following cytokine treatment, media was removed and cells were lysed using a guanidium thiocyanate solution. Total RNA was isolated from the cell lysate by an overnight spin on a cesium chloride gradient. The following day, the RNA pellet was resuspended in a TE/SDS solution and ethanol precipitated. RNA was then quantitated using a spectrophotometer, followed by a DNase treatment as per Section V.B. of Clontech's Atlas™ cDNA Expression Arrays User Manual (version PT3140-1/PR9X390, published 11/5/99). Quality of RNA samples was verified by purity calculations based on spec readings, and by visualization on agarose gel. Genomic contamination of the RNA samples was ruled out by PCR analysis of the beta-actin gene.

Probe Synthesis

Clontech's protocols for polyA+ enrichment, probe synthesis and hybridization to Atlas™ arrays were followed (see above, plus Atlas™ Pure Total RNA Labeling System User Manual, PT3231-1/PR96157, published 6/22/99). Briefly, polyA+ RNA was isolated from 50 mg of total RNA using streptavidin coated magnetic beads (by Clontech, Paolo Alto, CA) and a magnetic particle separator. PolyA+ RNA was then labeled with ^{alpha32}P-dATP via RT-PCR. Clontech CDS primers specific to the 268 genes on the Atlas™ human cytokine/receptor array (Cat. #7744-1) were used in the reaction. Labeled probe was isolated using column chromatography and counted in scintillation fluid.

Array membrane Hybridization

Atlas™ arrays were pre-hybridized with Clontech ExpressHyb plus 100 mg/mL heat denatured salmon sperm DNA for at least thirty minutes at 68°C with continuous agitation. Membranes were then hybridized with 1.9 x 10^6 CPM/mL (a total of 1.14 x 10^7 CPM) overnight at 68°C with continuous agitation. The following day, membranes were washed for thirty minutes x 4 in 2X SSC, 1% SDS at 68° C, plus for thirty minutes x 1 in 0.1X SSC, 0.5% SDS at 68°C, followed by one final room temperature wash for five minutes in 2X SSC. Array membranes were then placed in Kodak plastic pouches sealed and exposed to a phosphor imager screen overnight at room temperature. The next day, phosphor screens were scanned on a phosphor imager and analyzed using Clontech's AtlasImage™ 1.0 software.

Results

<u>Genes Up-regulated by IL-20</u>

1. Tumor necrosis factor (TNF) was up-regulated 1.9-2.4 fold by IL-20.
2. Placental growth factors 1 & 2 (PLGF) were up-regulated 1.9-2.0 fold by IL-20.
3. Coagulating factor II receptor was up-regulated 2.0-2.5 fold by IL-20.
4. Calcitonin receptor was up-regulated 2.2-2.3 fold by IL-20.

5. TNF-inducible hyaluronate-binding protein TSG-6 was up-regulated 2.1-2.2 fold by IL-20.
6. Vascular endothelial growth factor (VEGF) receptor-1 precursor, tyrosine-protein kinase receptor (FLT-1) (SFLT) was up-regulated 2.1-2.7 fold by IL-20.
7. MRP-8 (calcium binding protein in macrophages MIF- related) was up-regulated 2.9-4.1 fold by IL-20.
8. MRP-14 (calcium binding protein in macrophages MIF-related) was up-regulated 3.0-3.8 fold by IL-20.
9. Relaxin H2 was up-regulated 3.14 fold by IL-20.
10. Transforming growth factor beta (TGFβ) receptor III 300 kDa was up-regulated 2.4-3.6 fold by IL-20.

<u>Genes Showing Synergy with IL-20 + IL-1 Treatment</u>

1. Bone morphogenic protein 2a was up-regulated 1.8 fold with IL-20 treatment alone, 2.5 fold with IL-1 treatment alone, and 8.2 fold with both IL-20 and IL-1 treatment together.
2. MRP-8 was up-regulated 2.9 fold with IL-20 treatment alone, 10.7 fold with IL-1 treatment alone and 18.0 fold with both IL-20 and IL-1 treatment together.
3. Erythroid differentiation protein (EDF) was up-regulated 1.9 fold with IL-20 treatment alone, 9.7 fold with IL-1 treatment alone and 19.0 fold with both IL-20 and IL-1 treatment together.
4. MRP-14 (calcium binding protein in macrophages, MIF related) was up-regulated 3.0 fold with IL-20 treatment alone, 12.2 fold with IL-1 treatment alone and 20.3 fold with both IL-20 and IL-1 treatment together.
5. Heparin-binding EGF-like growth factor was up-regulated 2.0 fold with IL-20 treatment alone, 14 fold with IL-1 treatment alone and 25.0 fold with both IL-20 and IL-1 treatment together.
6. Beta-thromboglobulin-like protein was up-regulated 1.5 fold with IL-20 treatment alone, 15 fold with IL-1 treatment alone and 27 fold with both IL-20 and IL-1 treatment together.

7. Brain-derived neurotrophic factor (BDNF) was up-regulated 1.7 fold with IL-20 treatment alone, 25 fold with IL-1 treatment alone and 48 fold with both IL-20 and IL-1 treatment together.
8. Monocyte chemotactic and activating factor MCAF was up-regulated 1.3 fold with IL-20 treatment alone, 32 fold with IL-1 treatment alone and 56 fold with both IL-20 and IL-1 treatment together.

Example 5

IL-20RA/RB receptor-Ig fusion Heterotetramer

The expression vector pEZE3 was used to express the recombinant IL-20 receptor-Ig fusion protein. The plasmid pEZE3 is derived from pDC312. pDC312 was obtained through license from Immunex Corporation. The plasmids pDC312 and pEZE3 contain an EASE segment as described in WO 97/25420. The presence of the EASE segment in an expression vector can improve expression of recombinant proteins two to eight fold in stable cell pools.

The plasmid pEZE3 is a tricistronic expression vector that may be used to express up to three different proteins in mammalian cells, preferably Chinese Hamster Ovary (CHO) cells. The pEZE3 expression unit contains the cytomegalovirus (CMV) enhancer/promoter, the adenovirus tripartite leader sequence, a multiple cloning site for insertion of the coding region for the first recombinant protein, the poliovirus type 2 internal ribosome entry site, a second multiple cloning site for insertion of the coding region for the second recombinant protein, an encephalomyocarditis virus internal ribosome entry site, a coding segment for mouse dihydrofolate reductase, and the SV40 transcription terminator. In addition, pEZE3 contains an E. coli origin of replication and the bacterial beta lactamase gene.

The IL-20 receptor-Ig fusion protein is a disulfide linked heterotetramer consisting of two chains of the extracellular domain of the human IL-20RB fused to the wild type human immunoglobulin kappa light chain constant region and two chains of the human IL-20RA protein extracellular domain fused to a mutated human immunoglobulin gamma 1 constant region. The human immunoglobulin gamma 1

constant region contains amino acid substitutions to reduce FcγRI binding and C1q complement fixation.

The human IL-20RB extracellular domain human immunoglobulin kappa light chain constant region fusion construct was generated by overlap PCR. The IL-20RB coding segment consists of amino acids 1 to 230. The template used for the PCR amplification of the IL-20R segment was generated IL-20RB human kappa light chain constant region expression construct as described below in Example 12. Oligonucleotide primers SEQ ID NO: 24 and SEQ ID NO: 25 were used to amplify the IL-20RB segment. The entire wild type human immunoglobulin kappa light chain constant region was used. The template used for the PCR amplification of the wild type human immunoglobulin kappa light chain constant region segment was generated IL-20RB human kappa light chain constant region expression construct as described in Example 12. Oligonucleotide primers SEQ ID NO: 26 and SEQ ID NO: 27 were used to amplify the wild type human immunoglobulin kappa light chain constant region. The two protein coding domains were linked by overlap PCR using oligonucleotides SEQ ID NO: 24 and SEQ ID NO: 27. A $(Gly_4Ser)_3$ (SEQ ID NO: 72) peptide linker was inserted between the two protein domains. The $(Gly_4Ser)_3$ peptide linker was encoded on the PCR primers SEQ ID NO: 26 and SEQ ID NO:25. The resultant IL-20RB extracellular domain/kappa light chain constant region fusion construct is shown by SEQ ID NOs: 20 and 21. The predicted mature polypeptide, minus the signal sequence, is SEQ ID NO: 60. The portion of the extracellular domain of IL-20RB that was actually used was comprised of the amino acid sequence of SEQ ID NO: 61. N-terminal sequencing resulted in the predicted amino acid sequence.

The human IL-20RA extracellular domain human immunoglobulin gamma 1 heavy chain constant region fusion construct was generated by overlap PCR of four separate DNA fragments, each generated by separate PCR amplification reactions. The first fragment contained an optimized tPA (tissue plasminogen activator) signal sequence. The tPA signal sequence was amplified using oligonucleotide primers SEQ ID NO: 28 and SEQ ID NO: 29 using an in-house previously generated expression vector as the template. The second fragment contained the IL-20RA extracellular domain-coding region consisting of amino acids 30 to 243 of SEQ ID NO: 11.

Oligonucleotide primers SEQ ID NO: 30 and SEQ ID NO: 31 were used to amplify this IL-20RA segment using a previously generated clone of IL-20RA as the template.

The human gamma 1 heavy chain constant region was generated from 2 segments. The first segment containing the C_H1 domain was amplified using oligonucleotide primers SEQ ID NO: 32 and SEQ ID NO: 33 using a clone of the wild type human gamma 1 heavy chain constant region as the template. The second segment containing the remaining hinge, C_H2, and C_H3 domains of the human immunoglobulin gamma 1 heavy chain constant region was generated by PCR amplification using oligonucleotide primers SEQ ID NO: 34 and SEQ ID NO: 35. The template used for this PCR amplification was from a previously generated human gamma 1 Fc construct that contained codons for amino acid substitutions to reduce FcγRI binding and C1q complement fixation as described in Example 12.

The four protein coding domains were linked by overlap PCR using oligonucleotides SEQ ID NO: 28 and SEQ ID NO: 35. A $(Gly_4Ser)_3$ peptide linker was inserted between the IL-20RA and CH1 protein domains. The $(Gly_4Ser)_3$ peptide linker was encoded on the PCR primers SEQ ID NO: 32 and SEQ ID NO: 31. The IL-20RA extracellular domain/ domain human immunoglobulin gamma 1 heavy constant region fusion protein and DNA sequence are shown in SEQ ID NOs: 22 and 23. The predicted mature polypeptide sequence, minus the signal sequence, is SEQ ID NO: 62. The portion of extracellular domain of IL-20RA that was actually used was comprised of SEQ ID NO: 63.

The IL-20RB extracellular domain human immunoglobulin kappa light chain constant region fusion coding segment was cloned into the second MCS while the human IL-20RA extracellular domain human immunoglobulin gamma 1 heavy chain constant region fusion coding segment was cloned into the first MCS of pEZE3. The plasmid was used to transfect CHO cells. The cells were selected in medium without hypoxanthine or thymidine and the transgene was amplified using methotrexate. The presence of protein was assayed by Western blotting using anti human gamma 1 heavy chain constant region and anti human kappa light chain antibodies. N-terminal sequencing revealed that the optimized tPA leader was not completely cleaved. The observed mass indicated that the first residue of the polypeptide sequence to be

pyroglutamic acid, and the N-terminal sequence appears to be pyroEEIHAELRRFRRVPCVSGG (SEQ ID NO: 64), the underlined portion being remnants of the tPA leader.

Example 6

IL-20 Transgenic Phenotype

Both human and mouse IL-20 were overexpressed in transgenic mice using a variety of promoters. The liver-specific mouse albumin promoter, directing expression of human IL-20, was used initially in an attempt to achieve circulating levels of protein. Subsequent studies were conducted using the keratin 14 (K14) promoter, which primarily targets expression to the epidermis and other stratified squamous epithelia; the mouse metallothionein-1 promoter, which gives a broad expression pattern; and the EμLCK promoter, which drives expression in cells of the lymphoid lineage. Similar results were obtained in all four cases, possibly because these promoters all give rise to circulating levels of IL-20.

In all cases, transgenic pups expressing the IL-20 transgene were smaller than non-transgenic littermates, had a shiny appearance with tight, wrinkled skin and died within the first few days after birth. Pups had milk in their stomachs indicating that they were able to suckle. These mice had swollen extremities, tail, nostril and mouth regions and had difficulty moving. In addition, the mice were frail, lacked visible adipose tissue and had delayed ear and toe development. Low expression levels in liver (less than 100 mRNA molecules/cell) were sufficient for both the neonatal lethality and skin abnormalities. Transgenic mice without a visible phenotype either did not express the transgene, did not express it at detectable levels, or were mosaic.

Histologic analysis of the skin of the IL-20 transgenic mice showed a thickened epidermis, hyperkeratosis and a compact stratum corneum compared to non-transgenic littermates. Serocellular crusts (scabs) were observed occasionally. Electron microscopic (EM) analysis of skin from transgenic mice showed intramitochondrial lipoid inclusions, mottled keratohyaline granules, and relatively few tonofilaments similar to that observed in human psoriatic skin and in mouse skin disease models. In addition, many of the transgenic mice had apoptotic thymic lymphocytes. No other abnormalities were detected by histopathological analysis. These histological and EM

results support and extend the observed gross skin alterations.

Example 7

Specificity and Affinity of IL-20 for Its Receptor

The specificity and affinity of IL-20 for its receptor was determined using BHK cells stably transfected with IL-20RA, IL-20RB or both receptor subunits. Binding assays using radiolabeled ligand demonstrated that IL-20 bound to BHK transfectants expressing both IL-20RA and IL-20RB but not to untransfected cells nor to transfectants expressing either receptor subunit alone. Binding of ^{125}I-labeled IL-20 was eliminated in the presence of 100-fold excess of unlabeled IL-20 but not with 100-fold excess of the unrelated cytokine, IL-21. The binding affinity (k_D) of IL-20 to the IL-20RA/IL-20RB heterodimeric receptor was determined to be approximately 1.5 nM.

Example 8

IL-20 receptor Activation

To determine if IL-20 binding leads to receptor activation, the factor-dependent pre-B cell line BaF3 was co-transfected with IL-20RA and IL-20RB and treated with IL-20 at various concentrations. IL-20 stimulated proliferation in a dose-dependent manner and gave a detectable signal at 1.1 pM, with a half maximal response at 3.4 pM. We note that the IL-20 concentration for the half maximal proliferative response in BaF3 cells is 1000X lower than that for half maximal binding affinity in BHK cells. Possible explanations for this large difference include the use of different cell lines, different receptor expression levels and different assay outputs. IL-20 also stimulated signal transduction in the biologically relevant human keratinocyte cell line HaCaT, which naturally expresses IL-20RA and IL-20RB. Therefore, IL-20 binds and activates the heterodimeric IL-20RA/IL-20RB receptor at concentrations expected for a cytokine. While the negative controls containing untransfected BaF3

Example 9

Expression Analysis of IL-20RA and IL-20RB

RT-PCR analysis was performed on a variety of human tissues to determine the expression pattern of IL-20RA and IL-20RB. Both receptor subunits are most highly expressed in skin and testis. The significant result is that IL-20RA and IL-20RB are both expressed in skin, where they have been shown to mediate the IL-20-induced response. Both IL-20RA and IL-20RB are also both expressed in monocytes, lung, ovary, muscle, testis, adrenal gland, heart, salivary gland and placenta. IL-20RA is also in brain, kidney, liver, colon, small intestine, stomach, thyroid, pancreas, uterus and prostate while IL-20RB is not.

Example 10

IL-20RA and IL-20RB mRNA are Up-regulated in Psoriasis

In situ hybridization was used to determine whether IL-20 receptor expression is altered in psoriasis. Skin samples from four psoriasis patients and three unaffected patients were assayed with probes specific for the two-receptor subunit mRNAs. All four psoriatic skin samples had high levels of IL-20RA and IL-20RB mRNA in keratinocytes whereas normal skin samples did not have detectable levels of either receptor subunit mRNA. Positive signals in psoriatic skin were also observed in mononuclear immune cells and in endothelial cells in a subset of vessels. Therefore, both IL-20RA and IL-20RB are expressed in keratinocytes, immune cells and endothelial cells, the major cell types thought to interact in psoriasis.

Example 11

Cloning of Mouse IL-20RA

A cross-species hybridization probe was generated which contained the full-length cDNA fragment encoding human IL-20RA. A Southern blot of mouse genomic DNA and Northern blots of mouse RNA were performed to demonstrate that the human IL-20RA cDNA could specifically hybridize to mouse sequences. The Northern blot results indicated that mouse IL-20RA RNA was present in mouse embryo

day 15 and 17 as well as heart, brain, lung, liver, kidney, testes, spleen, thymus, liver, stomach, and small intestine.

The human IL-20RA full length DNA hybridization probe was used to screen a mouse genomic library. The library, which was obtained from Clontech (Palo Alto, CA), was generated from an MboI partial digest of mouse genomic DNA and cloned into the BamHI site of Lambda bacteriophage EMBL3 SP6/T7. Positive bacteriophage was plaque purified and bacteriophage DNA was prepared using Promega's Wizard Lambda Preps DNA Purification System. Two genomic restriction enzyme fragments, a 5.7 kb EcoRI fragment and an 8.0 kb SacI fragment, were generated from the positive bacteriophage and subcloned into pBluescript. DNA sequence analysis revealed the presence of 3 exons from the mouse ortholog to human IL-20RA.

PCR primers from the 5' UTR, SEQ ID NO: 40, and 3' UTR, SEQ ID NO: 41, were designed to generate a full-length mouse IL-20RA sequence by PCR amplification. Mouse embryo 15day plus 17 day cDNA was used as the template for the PCR amplification. PCR products were subcloned and sequenced for confirmation. The mouse sequences are SEQ ID NOs: 36 and 37. The mature extracellular domain is comprised of SEQ ID NO: 38.

Example 12

Construction of an IL-20 Receptor Heterotetramer

A vector expressing a secreted hIL-20RA/hIL-20B heterodimer was constructed. In this construct, the extracellular domain of hIL-20RA was fused to the heavy chain of IgG gamma 1 (IgGγ1), while the extracellular portion of IL-20RB was fused to human kappa light chain (human κ light chain).

Construction of IgG gamma 1 and human κ light fusion vectors

The heavy chain of IgGγ1 was cloned into the Zem229R mammalian expression vector (ATCC deposit No. 69447) such that any extracellular portion of a receptor having a 5' EcoRI and 3' NheI site can be cloned in, resulting in an N-terminal extracellular domain-C-terminal IgGγ1 fusion. The IgGγ1 fragment used in this construct was made by using PCR to isolate the IgGγ1 sequence from a Clontech

human fetal liver cDNA library as template. A PCR reaction using oligos SEQ ID NO: 42 and SEQ ID NO: 43 was run as follows: 40 cycles of 94° for 60 sec., 53°C for 60 sec., and 72° for 120 sec.; and 72°C for 7 minutes. PCR products were separated by agarose gel electrophoresis and purified using a QiaQuick™ (Qiagen Inc., Valencia, CA) gel extraction kit. The isolated, 990 bp, DNA fragment was digested with MluI and EcoRI (Boerhinger-Mannheim), extracted with QiaQuick™ gel extraction kit and ligated with oligos SEQ ID NO: 44 and SEQ ID NO: 45, which comprise an MluI/EcoRI linker, into Zem229R previously digested with MluI and EcoRI using standard molecular biology techniques disclosed herein. This generic cloning vector was called Vector#76 hIgGgamma1 w/ Ch1 #786 Zem229R (Vector #76). The polynucleotide sequence of the extracellular domain of hIL-20RA fused to the heavy chain of IgG gamma 1 is show in SEQ ID NO: 52 and the corresponding polypeptide sequence shown in SEQ ID NO: 53, the mature polypeptide, minus the signal sequence being comprised of SEQ ID NO: 54. The portion of the extracellular domain of IL-20RA used was comprised of SEQ ID NO: 55.

The human κ light chain was cloned in the Zem228R mammalian expression vector (ATCC deposit No. 69446) such that any extracellular portion of a receptor having a 5' EcoRI site and a 3' KpnI site can be cloned in, resulting in an N-terminal extracellular domain-C-terminal human κ light chain fusion. The human κ light chain fragment used in this construct was made by using PCR to isolate the human κ light chain sequence from the same Clontech hFetal Liver cDNA library used above. A PCR reaction was run using oligos SEQ ID NO: 46 and SEQ ID NO: 47. PCR products were separated by agarose gel electrophoresis and purified using a QiaQuick™ (Qiagen) gel extraction kit. The isolated, 315 bp, DNA fragment was digested with MluI and EcoRI (Boerhinger-Mannheim), extracted with QiaQuick™ gel extraction kit and ligated with the MluI/EcoRI linker described above, into Zem228R previously digested with MluI and EcoRI using standard molecular biology techniques disclosed herein. This generic cloning vector was called Vector #77 hκlight #774 Zem228R (Vector #77). The polynucleotide sequence of the extracellular portion of IL-20RB fused to human kappa light chain is shown in SEQ ID NO: 56 and the corresponding polypeptide sequence shown in SEQ ID NO: 57, the mature polypeptide, minus the

signal sequence, is comprised of SEQ ID NO: 58. The portion of the extracellular domain of IL-20RB actually used was comprised of SEQ ID NO: 59.

Insertion of hIL-20RA and IL-20RB extracellular domains into fusion vector constructs

Using the construction vectors above, a construct having human IL-20RA fused to IgGγ1 was made. This construction was done by using PCR to obtain human IL-20RA receptor from hIL-20RA /IgG Vector #102 with oligos SEQ ID NO: 48 and SEQ ID NO: 49 under conditions described as follows: 30 cycles of 94°C for 60 sec., 57°C for 60 sec., and 72°C for 120 sec.; and 72°C for 7 min. The resulting PCR product was digested with EcoRI and NheI, gel purified, as described herein, and ligated into a previously EcoRI and NheI digested and band-purified Vector #76 (above). The resulting vector was sequenced to confirm that the human IL-20Rα /IgG gamma 1 fusion (hIL-20RA /Ch1 IgG) was correct. The hIL-20RA /Ch1 IgG gamma 1 #1825 Zem229R vector was called vector #195. The IL-20RA/Ch1 IgGγ1 sequence thus obtained is depicted by SEQ ID NOs: 52 and 53. N-terminal sequencing indicated the presence of the predicted mature polypeptide sequence of SEQ ID NO: 54.

A separate construct having IL-20RB fused to κ light was also constructed. The IL-20RB/human κ light chain construction was performed as above by PCRing from DR1/7N-4 with oligos SEQ ID NO: 50 and SEQ ID NO: 51, digesting the resulting band with EcoRI and KpnI and then ligating this product into a previously EcoRI and KpnI digested and band-purified Vec#77 (above). The resulting vector was sequenced to confirm that the IL-20RB/ human κ light chain fusion (IL-20RB/κlight) was correct. This IL-20RB//κlight construct is shown by SEQ ID NOs: 56 and 57. N-terminal sequencing of the resultant polypeptide indicated the presence of the predicted mature amino acid sequence comprised of SEQ ID NO: 58. SEQ ID NO:59 is the mature portion of the extracellular domain of IL-20RB used.

Co-expression of the human IL-20RA and human IL-20RB receptors

Approximately 16μg of each of vectors #194 and #195, above, were co-transfected into BHK-570 cells (ATCC No. CRL-10314) using Lipofectamine™ reagent (Gibco/BRL), as per manufacturer's instructions. The transfected cells were selected

for 10 days in DMEM + 5%FBS (Gibco/BRL) containing 1μM of methotrexate (MTX) (Sigma, St. Louis, MO) and 0.5mg/ml G418 (Gibco/BRL) for 10 days. The resulting pool of transfectants was selected again in 10μM MTX and 0.5mg/ml G418 for 10 days.

The resulting pool of doubly selected cells was used to generate protein. Three factories (Nunc, Denmark) of this pool were used to generate 8 L of serum free conditioned medium. This conditioned media was passed over a 1 ml protein-A column and eluted in (10) 750 microliter fractions. 4 of these fractions found to have the highest concentration were pooled and dialyzed (10 kD MW cutoff) against PBS. Finally, the dialyzed material was analyzed by BCA (Pierce) and found to have a concentration of 317 μg/ml. A total of 951 μg was obtained from this 8 L purification.

Example 13

IL-20 Binding Activates STAT3 in the HaCaT Keratinocyte Cell Line

IL-20 binds cell lines transfected with both subunits of its receptor. However, these cell lines overexpress the IL-20 receptor relative to its normal level and their relevance to the physiological role of IL-20 is unclear. The human HaCaT keratinocyte cell line, which expresses endogenous IL-20RA and IL-20RB was used to examine IL-20 signal transduction in a biologically relevant cell type. HaCaT cells were infected with recombinant adenovirus containing a reporter construct to allow detection of intracellular signaling. The construct consists of the firefly luciferase gene driven by promoter/enhancer sequences comprised of the serum response element (SRE) and signal transducers and activators of transduction elements (STATs). This assay system detects productive ligand-receptor interactions and indicates possible downstream signal transduction components involved in receptor activation. Treatment with IL-20 alone resulted in a dose-dependent increase in luciferase activity with a half maximal response occurring at approximately 2.3 nM. Subsequent luciferase reporter assays using adenovirus vectors containing only the SRE element or only the STAT elements produced detectable reporter activation only through STATs .

To determine if other cytokines act in concert with IL-20, HaCaT cells were treated with IL-20 alone or in combination with a single submaximal dose of EGF,

IL-1β, or TNFα. In the presence of each of these three proteins, IL-20 treatment resulted in a dose-dependent increase in luciferase activity. IL-20 in combination with IL-1β results in a half-maximal response at approximately 0.5 nM, about five-fold lower than with IL-20 alone. In addition, activation of the reporter gene is detectable at 0.1 nM IL-20, a dose that is at least tenfold lower than the IL-20 dose required alone.

BHK cells transfected with IL-20RA, IL-20RB or both receptor subunits were used to determine whether receptor pairing was required for IL-20 stimulation of STAT-luciferase. As was the case with binding assays, only cells transfected with both receptor subunits responded to IL-20 and did so with a half-maximal response of 5.7 pM. We note that the IL-20 concentration for the half-maximal response in BHK cells is 400-fold lower than that for half-maximal response in HaCaT cells. It is likely that a lower concentration of IL-20 is needed for half-maximal response in BHK cells, as compared to HaCaT cells, due to higher receptor levels in the BHK IL-20 receptor transfectants.

A nuclear translocation assay was used to identify STAT proteins involved in IL-20 action. Both HaCaT cells, with endogenous IL-20 receptors, and BHK cells transfected with IL-20RA and IL-20RB, were treated with IL-20 protein and translocation of STAT3 and STAT1 transcription factors from the cytoplasm to the nucleus was assayed by immunofluorescence.

In unstimulated HaCaT cells, STAT3 staining was predominantly in the cytosol. Treatment of HaCaT cells with IL-20 resulted in a distinct accumulation of STAT3 in the nucleus. Nuclear translocation of STAT3 in response to increasing concentrations of IL-20 occurred with a half-maximal IL-20 concentration of 7 nM. In contrast to STAT3 translocation, HaCaT cells treated with IL-20 did not show any detectable nuclear accumulation of STAT1.

BHK cells transfected with IL-20RA and IL-20RB were used to confirm that the IL-20 receptor was required for IL-20 stimulation of STAT3 nuclear translocation. In BHK cells lacking the IL-20 receptor, STAT3 remained cytosolic following treatment with IL-20. In contrast, in BHK cells transfected with the IL-20 receptor, STAT3 translocated to the nucleus in response to IL-20. Again, STAT1

remained cytosolic regardless of IL-20 treatment or IL-20 receptor expression. We conclude that the IL-20 receptor is required for IL-20-mediated STAT3 activation.

WHAT IS CLAIMED IS:

1. A method for treating a mammal afflicted with a disease in which an IL-20 polypeptide plays a role, wherein the IL-20 polypeptide is comprised of an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8 and 9, comprising:

administering antagonist of said IL-20 polypeptide to said individual.

2. The method of claim 1 wherein the antagonist is selected from the group consisting of an antibody, antibody fragment or single chain antibody that binds to said IL-20 polypeptide, a soluble receptor that binds to said IL-20 polypeptide and an antibody, antibody fragment or single chain antibody which binds to the soluble receptor of IL-20 wherein said soluble receptor is comprised of an IL-20RA subunit and an IL-20RB subunit.

3. The method of claim 2 wherein the soluble receptor is a comprised of the extracellular domain of IL-20RA and the extracellular domain of IL-20RB.

4. The method of claim 3 wherein the extracellular domain of IL-20RA is fused to a constant region heavy chain of an immunoglobulin (Ig) molecule, and the extracellular domain of IL-20RB is fused to a constant region of a light chain of an Ig molecule.

5. The method of claim 2 wherein the antibody, antibody fragment or single chain antibody, which binds to the IL-20 receptor, binds to the IL-20RA subunit.

6. The method of claim 2 wherein the antibody, antibody fragment or single chain antibody, which binds to the IL-20 receptor, binds to the IL-20RB subunit.

7. The method of claim 1 wherein the disease that the IL-20 polypeptide plays a role is a skin disease selected from the group consisting of psoriasis, eczema, atopic dermatitis and contact dermatitis.

8. The method of claim 1 wherein the disease that the IL-20 polypeptide plays a role is an inflammatory lung selected from the group consisting of adult respiratory disease, asthma, bronchitis and pneumonia.

9. A method for promoting the expression of IL-8 in a cell comprising bringing the cell into contact with IL-20.

10. A method for increasing the expression of IL-8 in an individual comprising administering IL-20 to said individual.

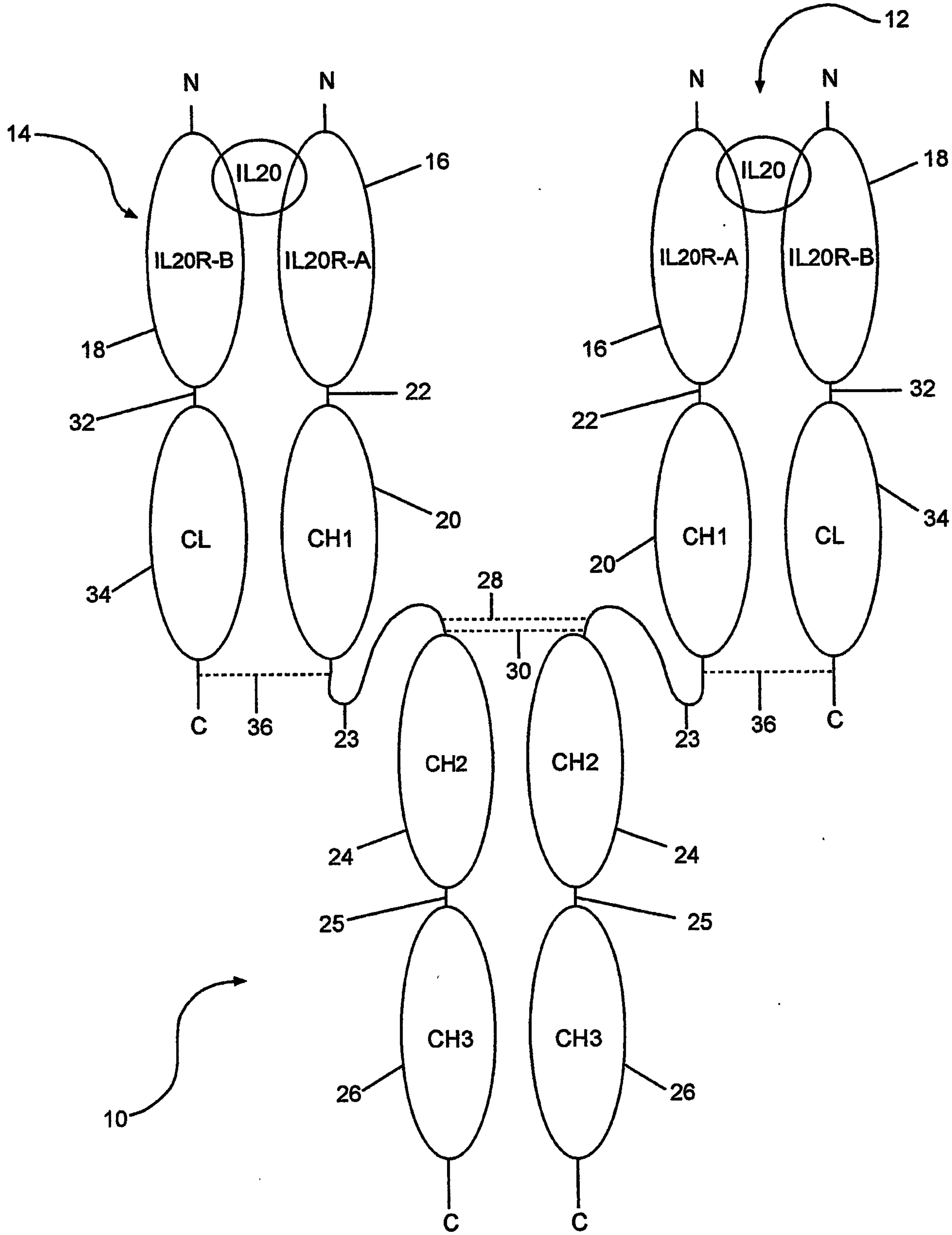
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FIG.1

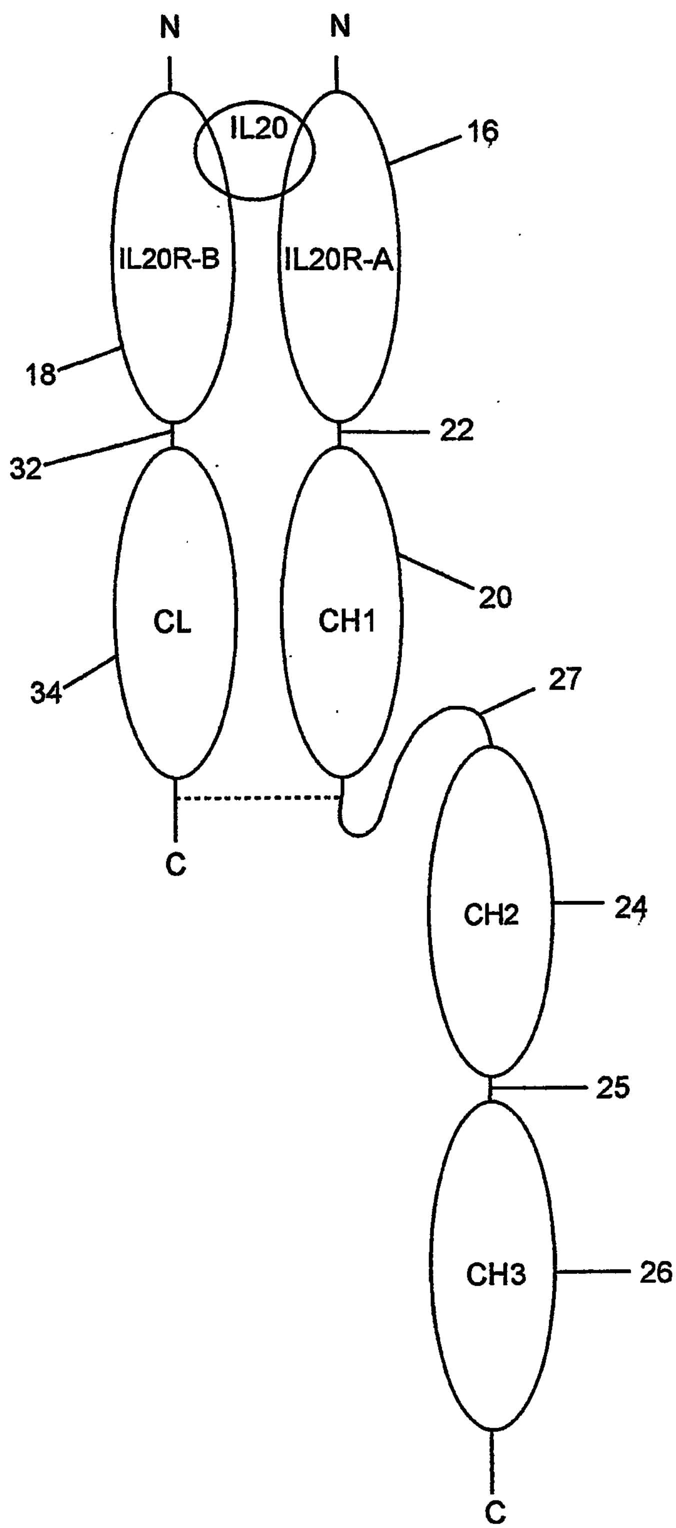
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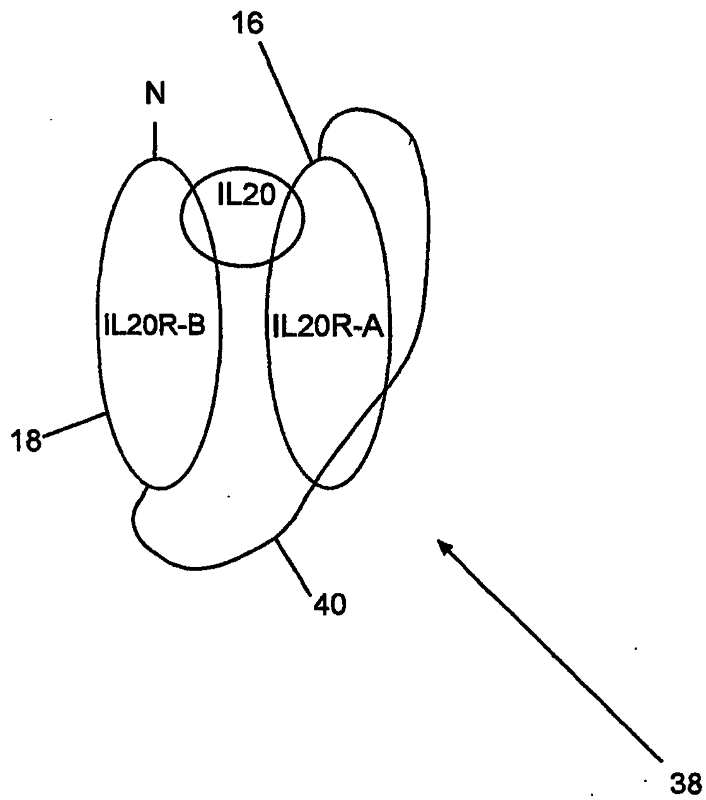
FIG.2



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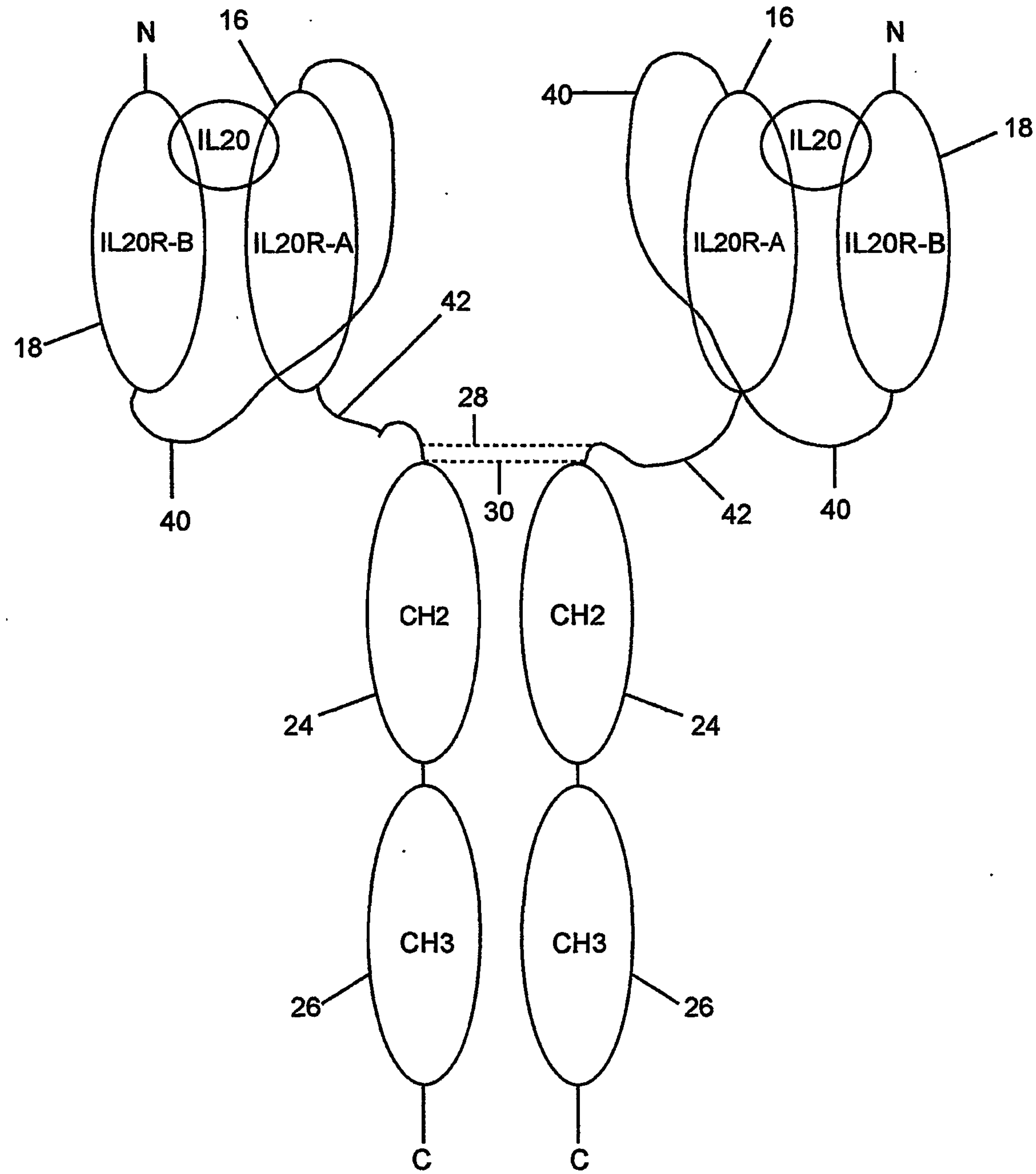
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FIG.4

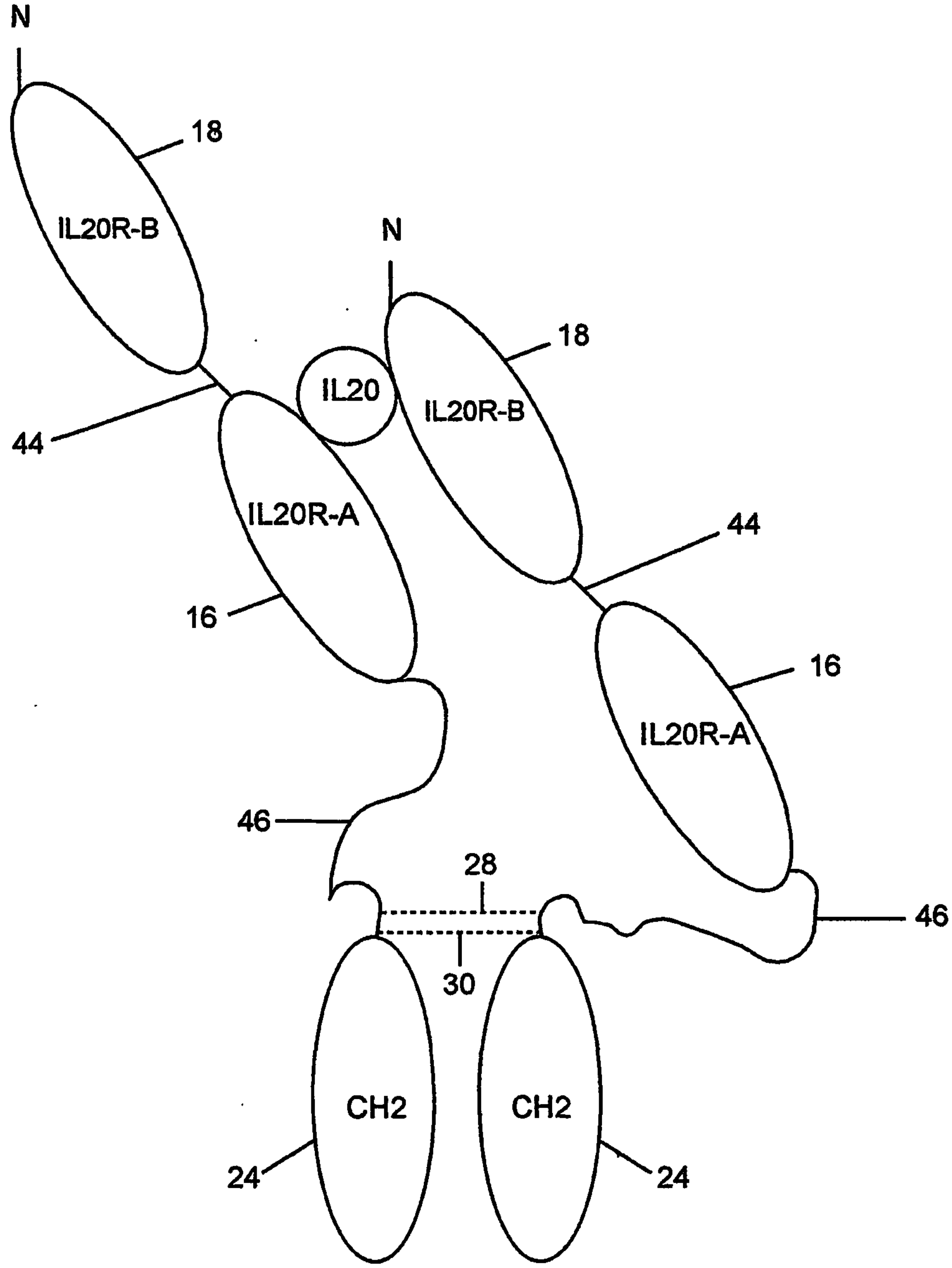
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FIG.5

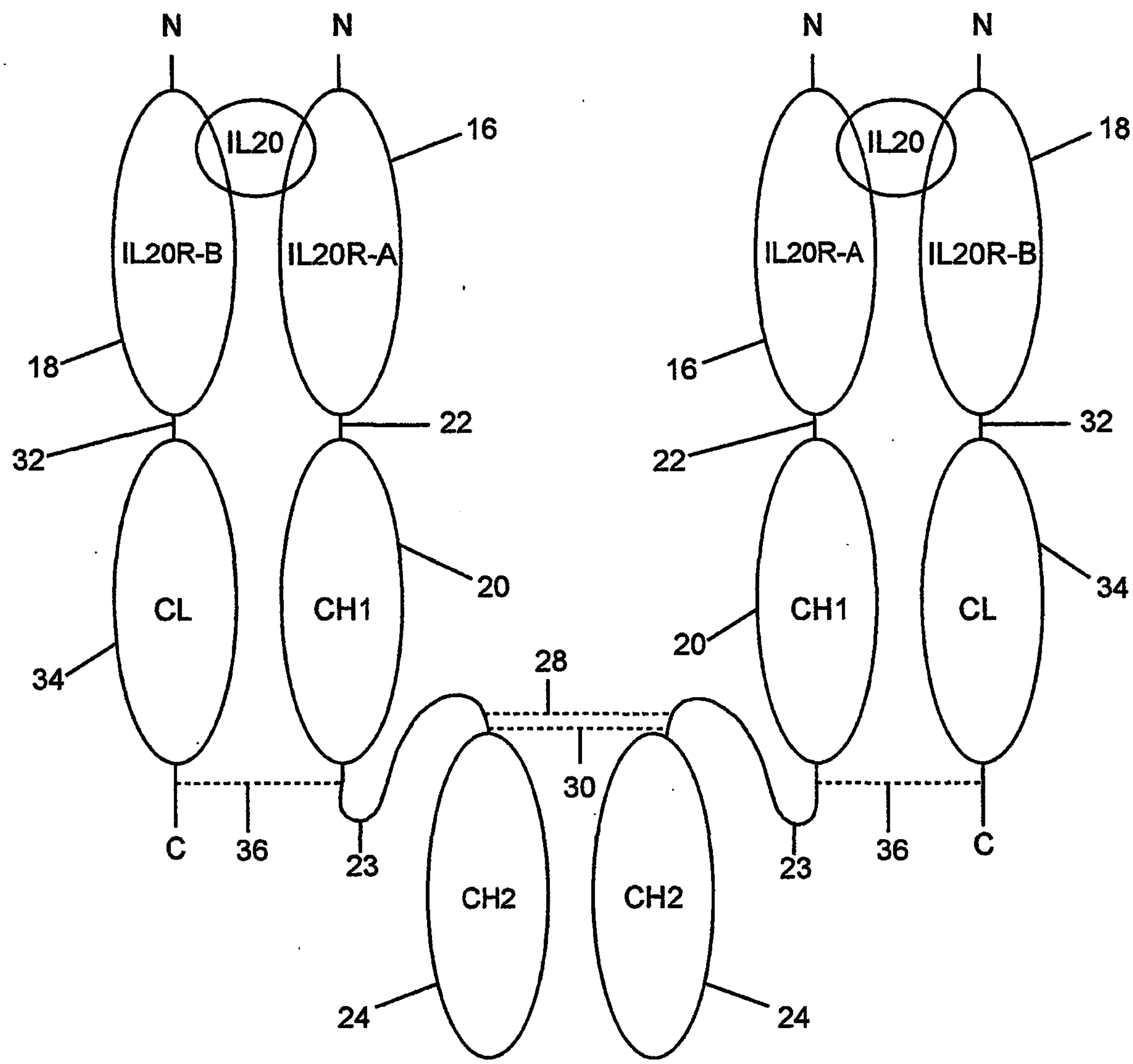
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FIG.6

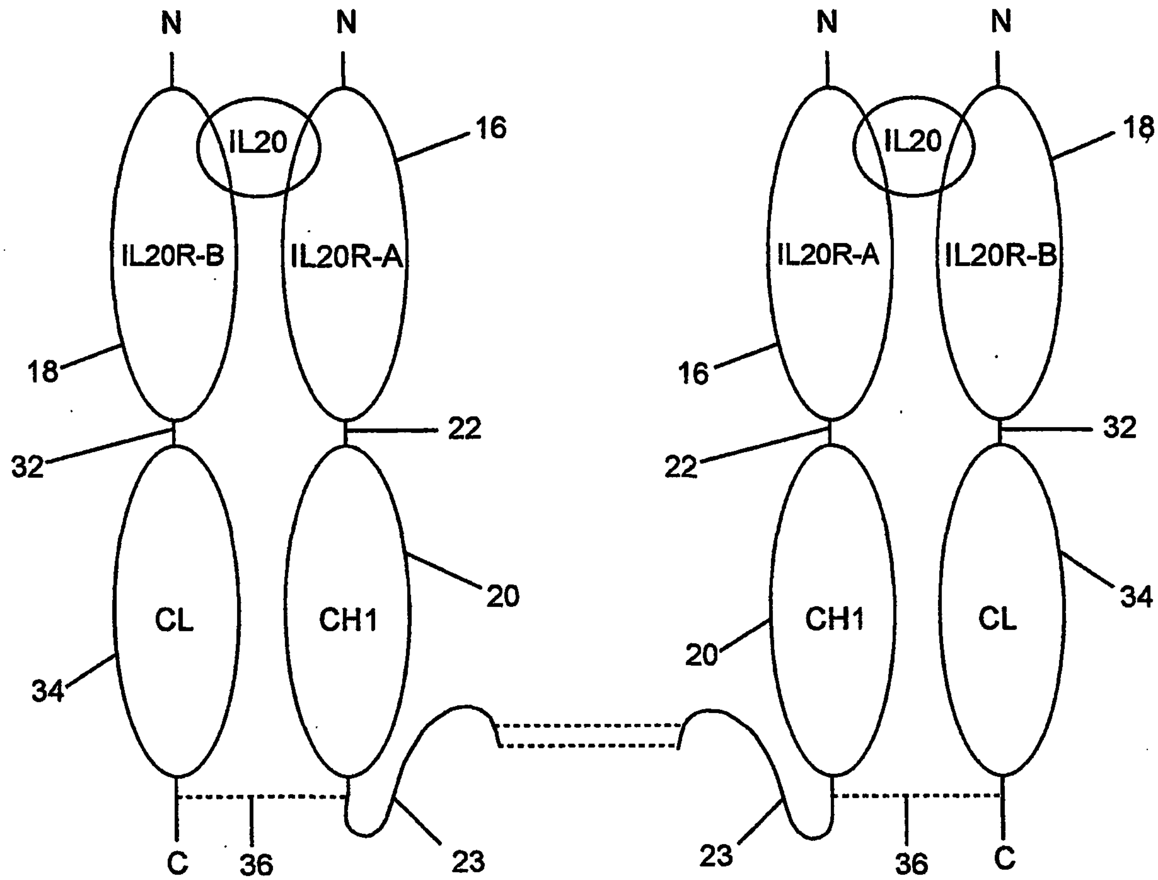
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FIG.7

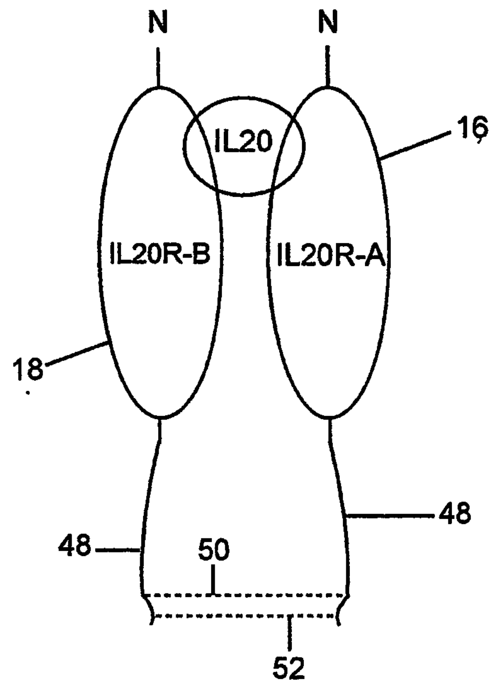

FIG.8

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aca gat gag aag tcc att tct gtt gtc ctg aca gct cca gag aag tgg     719
Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala Pro Glu Lys Trp
                150                 155                 160

aag aga aat cca gaa gac ctt cct gtt tcc atg caa caa ata tac tcc     767
Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln Gln Ile Tyr Ser
            165                 170                 175

aat ctg aag tat aac gtg tct gtg ttg aat act aaa tca aac aga acg     815
Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys Ser Asn Arg Thr
        180                 185                 190

tgg tcc cag tgt gtg acc aac cac acg ctg gtg ctc acc tgg ctg gag     863
Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu Thr Trp Leu Glu
    195                 200                 205

ccg aac act ctt tac tgc gta cac gtg gag tcc ttc gtc cca ggg ccc     911
Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe Val Pro Gly Pro
210                 215                 220                 225

cct cgc cgt gct cag cct tct gag aag cag tgt gcc agg act ttg aaa     959
Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala Arg Thr Leu Lys
                230                 235                 240

gat caa tca tca gag ttc aag gct aaa atc atc ttc tgg tat gtt ttg    1007
Asp Gln Ser Ser Glu Phe Lys Ala Lys Ile Ile Phe Trp Tyr Val Leu
            245                 250                 255

ccc ata tct att acc gtg ttt ctt ttt tct gtg atg ggc tat tcc atc    1055
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Pro Ile Ser Ile Thr Val Phe Leu Phe Ser Val Met Gly Tyr Ser Ile
260 265 270

tac cga tat atc cac gtt ggc aaa gag aaa cac cca gca aat ttg att 1103
Tyr Arg Tyr Ile His Val Gly Lys Glu Lys His Pro Ala Asn Leu Ile
275 280 285

ttg att tat gga aat gaa ttt gac aaa aga ttc ttt gtg cct gct gaa 1151
Leu Ile Tyr Gly Asn Glu Phe Asp Lys Arg Phe Phe Val Pro Ala Glu
290 295 300 305

aaa atc gtg att aac ttt atc acc ctc aat atc tcg gat gat tct aaa 1199
Lys Ile Val Ile Asn Phe Ile Thr Leu Asn Ile Ser Asp Asp Ser Lys
310 315 320

att tct cat cag gat atg agt tta ctg gga aaa agc agt gat gta tcc 1247
Ile Ser His Gln Asp Met Ser Leu Leu Gly Lys Ser Ser Asp Val Ser
325 330 335

agc ctt aat gat cct cag ccc agc ggg aac ctg agg ccc cct cag gag 1295
Ser Leu Asn Asp Pro Gln Pro Ser Gly Asn Leu Arg Pro Pro Gln Glu
340 345 350

gaa gag gag gtg aaa cat tta ggg tat gct tcg cat ttg atg gaa att 1343
Glu Glu Glu Val Lys His Leu Gly Tyr Ala Ser His Leu Met Glu Ile
355 360 365

ttt tgt gac tct gaa gaa aac acg gaa ggt act tct ttc acc cag caa 1391
Phe Cys Asp Ser Glu Glu Asn Thr Glu Gly Thr Ser Phe Thr Gln Gln
370 375 380 385

gag tcc ctc agc aga aca ata ccc ccg gat aaa aca gtc att gaa tat 1439
Glu Ser Leu Ser Arg Thr Ile Pro Pro Asp Lys Thr Val Ile Glu Tyr
390 395 400

gaa tat gat gtc aga acc act gac att tgt gcg ggg cct gaa gag cag 1487
Glu Tyr Asp Val Arg Thr Thr Asp Ile Cys Ala Gly Pro Glu Glu Gln
405 410 415

gag ctc agt ttg cag gag gag gtg tcc aca caa gga aca tta ttg gag 1535
Glu Leu Ser Leu Gln Glu Glu Val Ser Thr Gln Gly Thr Leu Leu Glu
420 425 430

tcg cag gca gcg ttg gca gtc ttg ggc ccg caa acg tta cag tac tca 1583
Ser Gln Ala Ala Leu Ala Val Leu Gly Pro Gln Thr Leu Gln Tyr Ser
435 440 445

tac acc cct cag ctc caa gac tta gac ccc ctg gcg cag gag cac aca 1631
Tyr Thr Pro Gln Leu Gln Asp Leu Asp Pro Leu Ala Gln Glu His Thr
450 455 460 465

gac tcg gag gag ggg ccg gag gaa gag cca tcg acg acc ctg gtc gac 1679
Asp Ser Glu Glu Gly Pro Glu Glu Glu Pro Ser Thr Thr Leu Val Asp
470 475 480

tgg gat ccc caa act ggc agg ctg tgt att cct tcg ctg tcc agc ttc 1727
Trp Asp Pro Gln Thr Gly Arg Leu Cys Ile Pro Ser Leu Ser Ser Phe
485 490 495

gac cag gat tca gag ggc tgc gag cct tct gag ggg gat ggg ctc gga 1775
Asp Gln Asp Ser Glu Gly Cys Glu Pro Ser Glu Gly Asp Gly Leu Gly
500 505 510

gag gag ggt ctt cta tct aga ctc tat gag gag ccg gct cca gac agg 1823
Glu Glu Gly Leu Leu Ser Arg Leu Tyr Glu Glu Pro Ala Pro Asp Arg
515 520 525

cca cca gga gaa aat gaa acc tat ctc atg caa ttc atg gag gaa tgg 1871
Pro Pro Gly Glu Asn Glu Thr Tyr Leu Met Gln Phe Met Glu Glu Trp
530 535 540 545

ggg tta tat gtg cag atg gaa aac tgatgccaac acttcctttt gccttttgtt 1925
Gly Leu Tyr Val Gln Met Glu Asn
550

tcctgtgcaa acaagtgagt caccccttg atcccagcca taaagtacct gggatgaaag 1985
aagtttttc cagtttgtca gtgtctgtga gaattactta tttcttttct ctattctcat 2045
agcacgtgtg tgattggttc atgcatgtag gtctcttaac aatgatggtg ggcctctgga 2105
gtccaggggc tggccggttg ttctatgcag agaaagcagt caataaatgt ttgccagact 2165
gggtgcagaa tttattcagg tgggtgtact ctggcctctt ggttcattat tttcaaacaa 2225
gcacacttgt acaattattt tctgggtact tcccatatgc acatagcact gtaaaaaata 2285
tttcccaaag atcactcatt ttataaatac cactttttca gaattgggtt tattgcgagc 2345
aggaggagat acttaaaaca tgcacatata ccaggttggt ggtaagttgg tcacatgtga 2405
aaacctcaac tatttaatca tcatgattca tattttgagt gaatacatca ggcacagacc 2465
ttcatgatat cacacactct tggctacttt aagaggccat ctttaatact ttatgagtag 2525
ttctggagtg taaacataaa cgagtattct tttgtagtca gaaaagtgtc ctctcaataa 2585

tttagtaggg gcttattgtc tctcaaaact aacctaaaag aaaatgacac attttataat 2645
agaatattac atttatttct ggaagtgtgt tttcaaaaag atatttacat agtctgtaaa 2705
ctagaaagtg ttaggtaaag ctctaggtta ctgtgttact attataatat taaacattcg 2765
aataggcagt cgttcaaaga ctctttggaa tatctatgaa tgaatatcct ctattcttat 2825
aatattaaaa cccataagta aatataggac atacaagaga aatgagttaa atgactatgt 2885
aagggagagt ttattaaaat ttgatgaaat ttactgtagg aactaaacta tgccataaaa 2945
caatagcttt ctagttcatt tccagtaact gttcccatct cctttaccac ttgttaagaa 3005
aattaaattc ttcagtcacg ctgctttaaa atgggacaaa atctattaag ttgaaccata 3065
tataattgtg gatatttggc tgtttttaat ctgacaagca gtaacttcat atggtttgcc 3125
ttaatatata tttgttttag tcatgaactc ataatccatt gatgctcttt catgagaaga 3185
gatatgaccc atatttcctt attgatatta ttggtacagg cagacaaccc tggtaggaga 3245
gatggattct ggggtcatga cctttcgtga ttatccgcaa atgcaaacag tttcagatct 3305
aatggtttaa tttagggagt aattatatta atcagagtgt tctgttattc tcaatcttta 3365
tagaaacgat tctgctggtt ttgaagaaca gatgtattac actaactgta aaagtagttc 3425
aagagtgaga aagaataaat tgttattaag agcaaaagaa aaataaagtg attgatgata 3485
aaaaaaaaaa aaaaaaagcg gccgcctcga g 3516

<210> 11
<211> 553
<212> PRT
<213> Homo sapiens

<400> 11
Met Arg Ala Pro Gly Arg Pro Ala Leu Arg Pro Leu Pro Leu Pro Pro
1 5 10 15
Leu Leu Leu Leu Leu Leu Ala Ala Pro Trp Gly Arg Ala Val Pro Cys
20 25 30
Val Ser Gly Gly Leu Pro Lys Pro Ala Asn Ile Thr Phe Leu Ser Ile
35 40 45
Asn Met Lys Asn Val Leu Gln Trp Thr Pro Pro Glu Gly Leu Gln Gly
50 55 60
Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys
65 70 75 80
Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr Tyr Cys Asp
85 90 95
Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr Ala Lys Val
100 105 110
Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu Ser Gly Arg
115 120 125
Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu Val Ala Leu
130 135 140
Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala Pro Glu Lys
145 150 155 160

Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln Gln Ile Tyr
165 170 175
Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys Ser Asn Arg
180 185 190
Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu Thr Trp Leu
195 200 205
Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe Val Pro Gly
210 215 220
Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala Arg Thr Leu
225 230 235 240
Lys Asp Gln Ser Ser Glu Phe Lys Ala Lys Ile Ile Phe Trp Tyr Val
245 250 255
Leu Pro Ile Ser Ile Thr Val Phe Leu Phe Ser Val Met Gly Tyr Ser
260 265 270
Ile Tyr Arg Tyr Ile His Val Gly Lys Glu Lys His Pro Ala Asn Leu
275 280 285
Ile Leu Ile Tyr Gly Asn Glu Phe Asp Lys Arg Phe Phe Val Pro Ala
290 295 300
Glu Lys Ile Val Ile Asn Phe Ile Thr Leu Asn Ile Ser Asp Asp Ser
305 310 315 320
Lys Ile Ser His Gln Asp Met Ser Leu Leu Gly Lys Ser Ser Asp Val
325 330 335
Ser Ser Leu Asn Asp Pro Gln Pro Ser Gly Asn Leu Arg Pro Pro Gln
340 345 350
Glu Glu Glu Glu Val Lys His Leu Gly Tyr Ala Ser His Leu Met Glu
355 360 365
Ile Phe Cys Asp Ser Glu Glu Asn Thr Glu Gly Thr Ser Phe Thr Gln
370 375 380
Gln Glu Ser Leu Ser Arg Thr Ile Pro Pro Asp Lys Thr Val Ile Glu
385 390 395 400
Tyr Glu Tyr Asp Val Arg Thr Thr Asp Ile Cys Ala Gly Pro Glu Glu
405 410 415
Gln Glu Leu Ser Leu Gln Glu Glu Val Ser Thr Gln Gly Thr Leu Leu
420 425 430
Glu Ser Gln Ala Ala Leu Ala Val Leu Gly Pro Gln Thr Leu Gln Tyr
435 440 445
Ser Tyr Thr Pro Gln Leu Gln Asp Leu Asp Pro Leu Ala Gln Glu His
450 455 460
Thr Asp Ser Glu Glu Gly Pro Glu Glu Glu Pro Ser Thr Thr Leu Val
465 470 475 480
Asp Trp Asp Pro Gln Thr Gly Arg Leu Cys Ile Pro Ser Leu Ser Ser
485 490 495

Phe Asp Gln Asp Ser Glu Gly Cys Glu Pro Ser Glu Gly Asp Gly Leu
500 505 510
Gly Glu Glu Gly Leu Leu Ser Arg Leu Tyr Glu Glu Pro Ala Pro Asp
515 520 525
Arg Pro Pro Gly Glu Asn Glu Thr Tyr Leu Met Gln Phe Met Glu Glu
530 535 540
Trp Gly Leu Tyr Val Gln Met Glu Asn
545 550

<210> 12
<211> 221
<212> PRT
<213> Homo sapiens

<400> 12
Val Pro Cys Val Ser Gly Gly Leu Pro Lys Pro Ala Asn Ile Thr Phe
1 5 10 15
Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp Thr Pro Pro Glu Gly
20 25 30
Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
35 40 45
Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr
50 55 60
Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr
65 70 75 80
Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu
85 90 95
Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu
100 105 110
Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala
115 120 125
Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln
130 135 140
Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys
145 150 155 160
Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu
165 170 175
Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe
180 185 190
Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala
195 200 205
Arg Thr Leu Lys Asp Gln Ser Ser Glu Phe Lys Ala Lys
210 215 220

<210> 13
<211> 971
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (18)...(950)

<400> 13
gaattcgagt ctaccaa atg cag act ttc aca atg gtt cta gaa gaa atc 50
Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile
1 5 10

tgg aca agt ctt ttc atg tgg ttt ttc tac gca ttg att cca tgt ttg 98
Trp Thr Ser Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu
15 20 25

ctc aca gat gaa gtg gcc att ctg cct gcc cct cag aac ctc tct gta 146
Leu Thr Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val
30 35 40

ctc tca acc aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg 194
Leu Ser Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala
45 50 55

cct gga gaa aca gtg tac tat tct gtc gaa tac cag ggg gag tac gag 242
Pro Gly Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu
60 65 70 75

agc ctg tac acg agc cac atc tgg atc ccc agc agc tgg tgc tca ctc 290
Ser Leu Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu
80 85 90

act gaa ggt cct gag tgt gat gtc act gat gac atc acg gcc act gtg 338
Thr Glu Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val
95 100 105

cca tac aac ctt cgt gtc agg gcc aca ttg ggc tca cag acc tca gcc 386
Pro Tyr Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala
110 115 120

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tgg agc atc ctg aag cat ccc ttt aat aga aac tca acc atc ctt acc      434
Trp Ser Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr
    125                 130                 135

cga cct ggg atg gag atc acc aaa gat ggc ttc cac ctg gtt att gag      482
Arg Pro Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu
140                 145                 150                 155

ctg gag gac ctg ggg ccc cag ttt gag ttc ctt gtg gcc tac tgg agg      530
Leu Glu Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg
                160                 165                 170

agg gag cct ggt gcc gag gaa cat gtc aaa atg gtg agg agt ggg ggt      578
Arg Glu Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly
            175                 180                 185

att cca gtg cac cta gaa acc atg gag cca ggg gct gca tac tgt gtg      626
Ile Pro Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val
        190                 195                 200

aag gcc cag aca ttc gtg aag gcc att ggg agg tac agc gcc ttc agc      674
Lys Ala Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser
    205                 210                 215

cag aca gaa tgt gtg gag gtg caa gga gag gcc att ccc ctg gta ctg      722
Gln Thr Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu
220                 225                 230                 235

gcc ctg ttt gcc ttt gtt ggc ttc atg ctg atc ctt gtg gtc gtg cca      770
Ala Leu Phe Ala Phe Val Gly Phe Met Leu Ile Leu Val Val Val Pro
                240                 245                 250

ctg ttc gtc tgg aaa atg ggc cgg ctg ctc cag tac tcc tgt tgc ccc      818
Leu Phe Val Trp Lys Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro
            255                 260                 265

gtg gtg gtc ctc cca gac acc ttg aaa ata acc aat tca ccc cag aag      866
Val Val Val Leu Pro Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Lys
        270                 275                 280

tta atc agc tgc aga agg gag gag gtg gat gcc tgt gcc acg gct gtg      914
Leu Ile Ser Cys Arg Arg Glu Glu Val Asp Ala Cys Ala Thr Ala Val
    285                 290                 295
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atg tct cct gag gaa ctc ctc agg gcc tgg atc tca taggtttgcg 960
Met Ser Pro Glu Glu Leu Leu Arg Ala Trp Ile Ser
300 305 310

gaaggctcga g 971

<210> 14
<211> 311
<212> PRT
<213> Homo sapiens

<400> 14
Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr Ser Leu Phe
1 5 10 15
Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
20 25 30
Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
35 40 45
Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
50 55 60
Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
65 70 75 80
His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
85 90 95
Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
100 105 110
Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
115 120 125
His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
130 135 140
Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
145 150 155 160
Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu Pro Gly Ala
165 170 175
Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
180 185 190
Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
195 200 205
Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
210 215 220
Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu Ala Leu Phe Ala Phe
225 230 235 240

Val Gly Phe Met Leu Ile Leu Val Val Val Pro Leu Phe Val Trp Lys
245 250 255
Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro Val Val Val Leu Pro
260 265 270
Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Lys Leu Ile Ser Cys Arg
275 280 285
Arg Glu Glu Val Asp Ala Cys Ala Thr Ala Val Met Ser Pro Glu Glu
290 295 300
Leu Leu Arg Ala Trp Ile Ser
305 310

<210> 15
<211> 203
<212> PRT
<213> Homo sapiens

<400> 15
Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
1 5 10 15
Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
20 25 30
Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
35 40 45
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
50 55 60
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
65 70 75 80
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
85 90 95
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
100 105 110
Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu
115 120 125
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu
130 135 140
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
145 150 155 160
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
165 170 175
Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
180 185 190
Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro
195 200

<210> 16
<211> 33
<212> DNA
<213> Homo sapiens

<400> 16
gcgaattcga gtctaccaaa tgcagacttt cac 33

<210> 17
<211> 32
<212> DNA
<213> Homo sapiens

<400> 17
cgctcgagcc ttccgcaaac ctatgagatc ca 32

<210> 18
<211> 1379
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (132)...(1034)

<400> 18
tcgacccacg cgtccgcgct gcgactcaga cctcagctcc aacatatgca ttctgaagaa 60
agatggctga gatggacaga atgctttatt ttggaaagaa acaatgttct aggtcaaact 120
gagtctacca a atg cag act ttc aca atg gtt cta gaa gaa atc tgg aca 170

Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr
1 5 10

agt ctt ttc atg tgg ttt ttc tac gca ttg att cca tgt ttg ctc aca 218
Ser Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr
15 20 25

gat gaa gtg gcc att ctg cct gcc cct cag aac ctc tct gta ctc tca 266
Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
30 35 40 45

acc aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga 314

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Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
                50                  55                  60

gaa aca gtg tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg      362
Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
            65                  70                  75

tac acg agc cac atc tgg atc ccc agc agc tgg tgc tca ctc act gaa      410
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
        80                  85                  90

ggt cct gag tgt gat gtc act gat gac atc acg gcc act gtg cca tac      458
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
    95                  100                 105

aac ctt cgt gtc agg gcc aca ttg ggc tca cag acc tca gcc tgg agc      506
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
110                 115                 120                 125

atc ctg aag cat ccc ttt aat aga aac tca acc atc ctt acc cga cct      554
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
                130                 135                 140

ggg atg gag atc ccc aaa cat ggc ttc cac ctg gtt att gag ctg gag      602
Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu
            145                 150                 155

gac ctg ggg ccc cag ttt gag ttc ctt gtg gcc tac tgg acg agg gag      650
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu
        160                 165                 170

cct ggt gcc gag gaa cat gtc aaa atg gtg agg agt ggg ggt att cca      698
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
    175                 180                 185

gtg cac cta gaa acc atg gag cca ggg gct gca tac tgt gtg aag gcc      746
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
190                 195                 200                 205

cag aca ttc gtg aag gcc att ggg agg tac agc gcc ttc agc cag aca      794
Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
                210                 215                 220
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gaa tgt gtg gag gtg caa gga gag gcc att ccc ctg gta ctg gcc ctg 842
Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu Ala Leu
225 230 235

ttt gcc ttt gtt ggc ttc atg ctg atc ctt gtg gtc gtg cca ctg ttc 890
Phe Ala Phe Val Gly Phe Met Leu Ile Leu Val Val Val Pro Leu Phe
240 245 250

gtc tgg aaa atg ggc cgg ctg ctc cag tac tcc tgt tgc ccc gtg gtg 938
Val Trp Lys Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro Val Val
255 260 265

gtc ctc cca gac acc ttg aaa ata acc aat tca ccc cag gtt aat cag 986
Val Leu Pro Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Val Asn Gln
270 275 280 285

ctg cag aag gga gga ggt gga tgc ctg tgc cac ggc tgt gat gtc tcc 1034
Leu Gln Lys Gly Gly Gly Gly Cys Leu Cys His Gly Cys Asp Val Ser
290 295 300

tgaggaactc ctcagggcct ggatctcata tcaggtttgc ggaagggccc aggtgaagcc 1094
gagaacctgg tctgcatgac atggaaacca tgaggggaca agttgtgttt ctgttttccg 1154
ccacggacaa gggatgagag aagtaggaag agcctgttgt ctacaagtct agaagcaacc 1214
atcagaggca gggtggtttg tctaacagaa caactgactg aggctatggg ggttgtgacc 1274
tctagacttt gggcttccac ttgcttggct gagcaaccct gggaaaagtg acttcatccc 1334
ttcggtccca agttttctca tctgtaatgg gggatcccta caaaactg 1382

<210> 19
<211> 301
<212> PRT
<213> Homo sapiens

<400> 19
Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr Ser Leu Phe
1 5 10 15
Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
20 25 30
Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
35 40 45
Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
50 55 60
Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
65 70 75 80

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His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
                85                  90                  95
Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
            100                 105                 110
Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
        115                 120                 125
His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
    130                 135                 140
Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
145                 150                 155                 160
Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro Gly Ala
                165                 170                 175
Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
            180                 185                 190
Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
        195                 200                 205
Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
    210                 215                 220
Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu Ala Leu Phe Ala Phe
225                 230                 235                 240
Val Gly Phe Met Leu Ile Leu Val Val Val Pro Leu Phe Val Trp Lys
                245                 250                 255
Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro Val Val Val Leu Pro
            260                 265                 270
Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Val Asn Gln Leu Gln Lys
        275                 280                 285
Gly Gly Gly Gly Cys Leu Cys His Gly Cys Asp Val Ser
    290                 295                 300

<210> 20
<211> 1081
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (9)...(1067)

<400> 20
ggccggcc atg cag act ttc aca atg gtt cta gaa gaa atc tgg aca agt      50
         Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr Ser
          1               5                  10
```

ctt ttc atg tgg ttt ttc tac gca ttg att cca tgt ttg ctc aca gat 98
Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp
15 20 25 30

gaa gtg gcc att ctg cct gcc cct cag aac ctc tct gta ctc tca acc 146
Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr
35 40 45

aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga gaa 194
Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu
50 55 60

aca gtg tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg tac 242
Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr
65 70 75

acg agc cac atc tgg atc ccc agc agc tgg tgc tca ctc act gaa ggt 290
Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly
80 85 90

cct gag tgt gat gtc act gat gac atc acg gcc act gtg cca tac aac 338
Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn
95 100 105 110

ctt cgt gtc agg gcc aca ttg ggc tca cag acc tca gcc tgg agc atc 386
Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile
115 120 125

ctg aag cat ccc ttt aat aga aac tca acc atc ctt acc cga cct ggg 434
Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly
130 135 140

atg gag atc ccc aaa cat ggc ttc cac ctg gtt att gag ctg gag gac 482
Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp
145 150 155

ctg ggg ccc cag ttt gag ttc ctt gtg gcc tac tgg acg agg gag cct 530
Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro
160 165 170

ggt gcc gag gaa cat gtc aaa atg gtg agg agt ggg ggt att cca gtg 578
Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val
175 180 185 190

```
cac cta gaa acc atg gag cca ggg gct gca tac tgt gtg aag gcc cag      626
His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln
                195                 200                 205

aca ttc gtg aag gcc att ggg agg tac agc gcc ttc agc cag aca gaa      674
Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu
            210                 215                 220

tgt gtg gag gtg caa gga gag gcc gga ggt ggt ggc agt gga ggc ggc      722
Cys Val Glu Val Gln Gly Glu Ala Gly Gly Gly Gly Ser Gly Gly Gly
        225                 230                 235

ggt agc gga ggc ggt ggc agt cga act gtg gct gca cca tct gtc ttc      770
Gly Ser Gly Gly Gly Gly Ser Arg Thr Val Ala Ala Pro Ser Val Phe
    240                 245                 250

atc ttc ccg cca tct gat gag cag ttg aaa tct gga act gcc tct gtt      818
Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
255                 260                 265                 270

gtg tgc ctg ctg aat aac ttc tat ccc aga gag gcc aaa gta cag tgg      866
Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
                275                 280                 285

aag gtg gat aac gcc ctc caa tcg ggt aac tcc cag gag agt gtc aca      914
Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
            290                 295                 300

gag cag gac agc aag gac agc acc tac agc ctc agc agc acc ctg acg      962
Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
        305                 310                 315

ctg agc aaa gca gac tac gag aaa cac aaa gtc tac gcc tgc gaa gtc     1010
Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
    320                 325                 330

acc cat cag ggc ctg agc tcg ccc gtc aca aag agc ttc aac agg gga     1058
Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
335                 340                 345                 350

gag tgt taa tctagaggcg cgcc                                         1081
Glu Cys  *
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<210> 21
<211> 352
<212> PRT
<213> Homo sapiens

<400> 21
Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr Ser Leu Phe
1 5 10 15
Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
20 25 30
Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
35 40 45
Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
50 55 60
Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
65 70 75 80
His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
85 90 95
Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
100 105 110
Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
115 120 125
His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
130 135 140
Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
145 150 155 160
Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro Gly Ala
165 170 175
Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
180 185 190
Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
195 200 205
Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
210 215 220
Glu Val Gln Gly Glu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
225 230 235 240
Gly Gly Gly Gly Ser Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
245 250 255
Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
260 265 270
Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
275 280 285

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
290 295 300
Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
305 310 315 320
Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
325 330 335
Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
340 345 350

<210> 22
<211> 1801
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (8)...(1789)

<400> 22
gtcgacc atg gat gca atg aag aga ggg ctc tgc tgt gtg ctg ctg ctg 49
Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu
1 5 10

tgt ggc gcc gtc ttc gtt tcg ctc agc cag gaa atc cat gcc gag ttg 97
Cys Gly Ala Val Phe Val Ser Leu Ser Gln Glu Ile His Ala Glu Leu
15 20 25 30

aga cgc ttc cgt aga gtt ccc tgt gtc tct ggt ggt ttg cct aaa cct 145
Arg Arg Phe Arg Arg Val Pro Cys Val Ser Gly Gly Leu Pro Lys Pro
35 40 45

gca aac atc acc ttc tta tcc atc aac atg aag aat gtc cta caa tgg 193
Ala Asn Ile Thr Phe Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp
50 55 60

act cca cca gag ggt ctt caa gga gtt aaa gtt act tac act gtg cag 241
Thr Pro Pro Glu Gly Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln
65 70 75

tat ttc ata tat ggg caa aag aaa tgg ctg aat aaa tca gaa tgc aga 289
Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg
80 85 90

aat atc aat aga acc tac tgt gat ctt tct gct gaa act tct gac tac 337
Asn Ile Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr
95 100 105 110

gaa cac cag tat tat gcc aaa gtt aag gcc att tgg gga aca aag tgt 385
Glu His Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys
115 120 125

tcc aaa tgg gct gaa agt gga cgg ttc tat cct ttt tta gaa aca caa 433
Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln
130 135 140

att ggc cca cca gag gtg gca ctg act aca gat gag aag tcc att tct 481
Ile Gly Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser
145 150 155

gtt gtc ctg aca gct cca gag aag tgg aag aga aat cca gaa gac ctt 529
Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu
160 165 170

cct gtt tcc atg caa caa ata tac tcc aat ctg aag tat aac gtg tct 577
Pro Val Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser
175 180 185 190

gtg ttg aat act aaa tca aac aga acg tgg tcc cag tgt gtg acc aac 625
Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn
195 200 205

cac acg ctg gtg ctc acc tgg ctg gag ccg aac act ctt tac tgc gta 673
His Thr Leu Val Leu Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val
210 215 220

cac gtg gag tcc ttc gtc cca ggg ccc cct cgc cgt gct cag cct tct 721
His Val Glu Ser Phe Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser
225 230 235

gag aag cag tgt gcc agg act ttg aaa gat caa ggt gga ggc ggt tca 769
Glu Lys Gln Cys Ala Arg Thr Leu Lys Asp Gln Gly Gly Gly Gly Ser
240 245 250

ggc gga ggt ggc tct ggc ggt ggc gga tcg gcc tcc acc aag ggc cca 817
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Thr Lys Gly Pro
255 260 265 270

```
tcg gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggg ggc aca      865
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
                275                 280                 285

gcg gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccg gtg acg      913
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
            290                 295                 300

gtg tcg tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccg      961
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
        305                 310                 315

gct gtc cta cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc     1009
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
    320                 325                 330

gtg ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat     1057
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
335                 340                 345                 350

cac aag ccc agc aac acc aag gtg gac aag aaa gtt gag ccc aaa tct     1105
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
                355                 360                 365

tgt gac aaa act cac aca tgc cca ccg tgc cca gca cct gaa gcc gag     1153
Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu
            370                 375                 380

ggg gca ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc     1201
Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
        385                 390                 395

atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc     1249
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
    400                 405                 410

cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag     1297
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
415                 420                 425                 430

gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg     1345
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Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
435 440 445

tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat 1393
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
450 455 460

ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca tcc tcc 1441
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser
465 470 475

atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag 1489
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
480 485 490

gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac cag gtc 1537
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
495 500 505 510

agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg 1585
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
515 520 525

gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct 1633
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
530 535 540

ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc 1681
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
545 550 555

gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg 1729
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
560 565 570

atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg 1777
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
575 580 585 590

tct ccg ggt aaa taatctagat ct 1801
Ser Pro Gly Lys

<210> 23

<211> 594
<212> PRT
<213> Homo sapiens

<400> 23
Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
1 5 10 15
Ala Val Phe Val Ser Leu Ser Gln Glu Ile His Ala Glu Leu Arg Arg
20 25 30
Phe Arg Arg Val Pro Cys Val Ser Gly Gly Leu Pro Lys Pro Ala Asn
35 40 45
Ile Thr Phe Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp Thr Pro
50 55 60
Pro Glu Gly Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln Tyr Phe
65 70 75 80
Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile
85 90 95
Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His
100 105 110
Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys
115 120 125
Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly
130 135 140
Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val
145 150 155 160
Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val
165 170 175
Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu
180 185 190
Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr
195 200 205
Leu Val Leu Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val
210 215 220
Glu Ser Phe Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys
225 230 235 240
Gln Cys Ala Arg Thr Leu Lys Asp Gln Gly Gly Gly Gly Ser Gly Gly
245 250 255
Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Thr Lys Gly Pro Ser Val
260 265 270
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
275 280 285
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
290 295 300

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
305 310 315 320
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
325 330 335
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
340 345 350
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
355 360 365
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala
370 375 380
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
385 390 395 400
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
405 410 415
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
420 425 430
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
435 440 445
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
450 455 460
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu
465 470 475 480
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
485 490 495
Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
500 505 510
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
515 520 525
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
530 535 540
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
545 550 555 560
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
565 570 575
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
580 585 590
Gly Lys

<210> 24
<211> 29
<212> DNA
<213> Homo sapiens

<400> 24
ggccggccat gcagactttc acaatggtt 29

<210> 25
<211> 52
<212> DNA
<213> homo sapiens

<400> 25
tccgctaccg ccgcctccac tgccaccacc tccggcctct ccttgcacct cc 52

<210> 26
<211> 53
<212> DNA
<213> Homo sapiens

<400> 26
gtggaggcgg cggtagcgga ggcggtggca gtcgaactgt ggctgcacca tct 53

<210> 27
<211> 38
<212> DNA
<213> Homo sapiens

<400> 27
ggcgcgcctc tagattaaca ctctcccctg ttgaagct 38

<210> 28
<211> 30
<212> DNA
<213> Homo sapiens

<400> 28
gtcgaccatg gatgcaatga agagagggct 30

<210> 29
<211> 30
<212> DNA
<213> Homo sapiens

<400> 29
cacagggaac tctacggaag cgtctcaact 30

<210> 30
<211> 33
<212> DNA
<213> Homo sapiens

<400> 30
cttccgtaga gttccctgtg tctctggtgg ttt 33

<210> 31
<211> 53
<212> DNA
<213> Homo sapiens

<400> 31
gccagagcca cctccgcctg aaccgcctcc accttgatct ttcaaagtcc tgg 53

<210> 32
<211> 51
<212> DNA
<213> Homo sapiens

<400> 32
caggcggagg tggctctggc ggtggcggat cggcctccac caagggccca t 51

<210> 33
<211> 20
<212> DNA
<213> Homo sapiens

<400> 33
ctgggcacgg tgggcatgtg 20

<210> 34
<211> 20
<212> DNA
<213> Homo sapiens

<400> 34
cacatgccca ccgtgcccag 20

<210> 35
<211> 31
<212> DNA

<213> Homo sapiens

<400> 35
agatctagat tatttacccg gagacaggga g 31

<210> 36
<211> 1806
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (38)...(1675)

<400> 36
cgccgcgttc ccgagatgtg acccgaactg acagccc atg cac act ccc ggg acc 55
Met His Thr Pro Gly Thr
1 5

ccg gcg ccg ggc cac ccg gac ccg ccg cca ctg ttg ctg ctc acg ctg 103
Pro Ala Pro Gly His Pro Asp Pro Pro Pro Leu Leu Leu Leu Thr Leu
10 15 20

ctt ctg ctg ctg gcc gct tcg gga cgc gca gtt cct tgt gtc ttc tgt 151
Leu Leu Leu Leu Ala Ala Ser Gly Arg Ala Val Pro Cys Val Phe Cys
25 30 35

ggt ttg cct aaa cct aca aat atc acc ttc tta tcc atc aac atg aag 199
Gly Leu Pro Lys Pro Thr Asn Ile Thr Phe Leu Ser Ile Asn Met Lys
40 45 50

aat gtc ctg cat tgg aat cca cca gag agt cta cac gga gtt gaa gtc 247
Asn Val Leu His Trp Asn Pro Pro Glu Ser Leu His Gly Val Glu Val
55 60 65 70

aca tac act gtg caa tat ttc ata tat ggg cag aag aaa tgg ctg aat 295
Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn
75 80 85

gcc tct aaa tgc ggg agt atc aac agg acc tac tgt gac ctt tct gtt 343
Ala Ser Lys Cys Gly Ser Ile Asn Arg Thr Tyr Cys Asp Leu Ser Val
90 95 100

gag acc tca gac tat gaa cac cag ttc tat gcc aaa gtg aag gcc att 391
Glu Thr Ser Asp Tyr Glu His Gln Phe Tyr Ala Lys Val Lys Ala Ile
105 110 115

tgg gaa gcc agg tgc tcc gaa tgg gcc gag acg gaa cgc ttc tat cct 439
Trp Glu Ala Arg Cys Ser Glu Trp Ala Glu Thr Glu Arg Phe Tyr Pro
120 125 130

ttc ttg gaa act caa gtc agc cca cca gag att gcc ctg aca act ggc 487
Phe Leu Glu Thr Gln Val Ser Pro Pro Glu Ile Ala Leu Thr Thr Gly
135 140 145 150

gag aag tcc atc tct att gcc ctg aca gca cca gag aag tgg aaa aga 535
Glu Lys Ser Ile Ser Ile Ala Leu Thr Ala Pro Glu Lys Trp Lys Arg
155 160 165

aat cca caa gac cac act gtt tct atg caa cag ata tac ccc aat ttg 583
Asn Pro Gln Asp His Thr Val Ser Met Gln Gln Ile Tyr Pro Asn Leu
170 175 180

aag tac aat gtg tct gtg tat aac act aag tcg aga aga acg tgg tcc 631
Lys Tyr Asn Val Ser Val Tyr Asn Thr Lys Ser Arg Arg Thr Trp Ser
185 190 195

cag tgt gtc acc aac agc aca ctg gtc ctc agc tgg ctg gag ccc aac 679
Gln Cys Val Thr Asn Ser Thr Leu Val Leu Ser Trp Leu Glu Pro Asn
200 205 210

act ctg tat tgt gtc cac gtg gag tcc ctt gtc cca ggg ccc cct cgc 727
Thr Leu Tyr Cys Val His Val Glu Ser Leu Val Pro Gly Pro Pro Arg
215 220 225 230

ctc ccg atg cct tct cag aag cag tgc atc agt act ttg gaa gtt caa 775
Leu Pro Met Pro Ser Gln Lys Gln Cys Ile Ser Thr Leu Glu Val Gln
235 240 245

aca tca gca tgg aag gct aaa gtc atc ttc tgg tat gtc ttc ctc aca 823
Thr Ser Ala Trp Lys Ala Lys Val Ile Phe Trp Tyr Val Phe Leu Thr
250 255 260

tct gtt atc gtg ttt ctt ttc tcc gca att ggc tac ttg gtt tac cgt 871
Ser Val Ile Val Phe Leu Phe Ser Ala Ile Gly Tyr Leu Val Tyr Arg
265 270 275

tac atc cat gtt ggc aag gaa aaa cac cca gca aat ttg gta ctg att 919
Tyr Ile His Val Gly Lys Glu Lys His Pro Ala Asn Leu Val Leu Ile
280 285 290

tat aga aat gaa att ggc aca aga gtc ttt gaa cct act gaa aca atc 967
Tyr Arg Asn Glu Ile Gly Thr Arg Val Phe Glu Pro Thr Glu Thr Ile
295 300 305 310

aca ctt aat ttt atc acc ttc agt atg ttg gat gat act aaa att tct 1015
Thr Leu Asn Phe Ile Thr Phe Ser Met Leu Asp Asp Thr Lys Ile Ser
315 320 325

cca aag gat atg aat tta ctg gac aaa agc agt gat gac atc agt gtt 1063
Pro Lys Asp Met Asn Leu Leu Asp Lys Ser Ser Asp Asp Ile Ser Val
330 335 340

aat gac cct gag cac aat gag gcc tgg gag ccg cac tgg gag gag gtg 1111
Asn Asp Pro Glu His Asn Glu Ala Trp Glu Pro His Trp Glu Glu Val
345 350 355

gag ggg caa cat tta gga tgc tct tcg cat ttg atg gac gct gtc tgt 1159
Glu Gly Gln His Leu Gly Cys Ser Ser His Leu Met Asp Ala Val Cys
360 365 370

ggt gct gag caa aga gac gga gac acc tcc cta acc cag cat ggg tgg 1207
Gly Ala Glu Gln Arg Asp Gly Asp Thr Ser Leu Thr Gln His Gly Trp
375 380 385 390

ctt aac agc acc atc ccc aca gga gag aca gac act gag cct caa tac 1255
Leu Asn Ser Thr Ile Pro Thr Gly Glu Thr Asp Thr Glu Pro Gln Tyr
395 400 405

aaa gtc cta agt gac ttc tac ggg gag ggt gaa atc caa ctg tcc tgt 1303
Lys Val Leu Ser Asp Phe Tyr Gly Glu Gly Glu Ile Gln Leu Ser Cys
410 415 420

gag ccg gaa gag gcg gcc aga aca gag aaa ata tct gag cca ctg gtg 1351
Glu Pro Glu Glu Ala Ala Arg Thr Glu Lys Ile Ser Glu Pro Leu Val
425 430 435

act tca gca aac ttg gac cca cag ctt gaa gac cta cat cac ctg ggt 1399

Thr Ser Ala Asn Leu Asp Pro Gln Leu Glu Asp Leu His His Leu Gly
440 445 450

cag gag cat act gtc tcc gag gat ggg cca gag gaa gag aca tct ata 1447
Gln Glu His Thr Val Ser Glu Asp Gly Pro Glu Glu Glu Thr Ser Ile
455 460 465 470

aca gta gtg gat tgg gac cct caa act ggc agg ctg tgt atc cct tcc 1495
Thr Val Val Asp Trp Asp Pro Gln Thr Gly Arg Leu Cys Ile Pro Ser
475 480 485

tta cct atc ttt ggc cgt gat cct gag aac tat ggt cat tat gag aga 1543
Leu Pro Ile Phe Gly Arg Asp Pro Glu Asn Tyr Gly His Tyr Glu Arg
490 495 500

gac cag ctc tta gag ggt ggc ctt ttg tct aga ctc tat gag aac cag 1591
Asp Gln Leu Leu Glu Gly Gly Leu Leu Ser Arg Leu Tyr Glu Asn Gln
505 510 515

gca cct gac aag cca gag aaa gaa aat gaa aac tgt ctc aca cgg ttt 1639
Ala Pro Asp Lys Pro Glu Lys Glu Asn Glu Asn Cys Leu Thr Arg Phe
520 525 530

atg gag gaa tgg ggg tta cat gta caa atg gaa agc tagtgccagg 1685
Met Glu Glu Trp Gly Leu His Val Gln Met Glu Ser
535 540 545

ctttctgttg actgccaaca aatgaaggaa ccatcccagg gggtgaacag tgttcaggtt 1745
atcagtgtca gcaatgagac tgttctctct gttcatgaac tttgtcagcc ctgcctcatc 1805
c 1806

<210> 37
<211> 546
<212> PRT
<213> Mus musculus

<400> 37
Met His Thr Pro Gly Thr Pro Ala Pro Gly His Pro Asp Pro Pro Pro
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Leu Leu Leu Leu Thr Leu Leu Leu Leu Leu Ala Ala Ser Gly Arg Ala
20 25 30
Val Pro Cys Val Phe Cys Gly Leu Pro Lys Pro Thr Asn Ile Thr Phe
35 40 45

Leu Ser Ile Asn Met Lys Asn Val Leu His Trp Asn Pro Pro Glu Ser
50 55 60
Leu His Gly Val Glu Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
65 70 75 80
Gln Lys Lys Trp Leu Asn Ala Ser Lys Cys Gly Ser Ile Asn Arg Thr
85 90 95
Tyr Cys Asp Leu Ser Val Glu Thr Ser Asp Tyr Glu His Gln Phe Tyr
100 105 110
Ala Lys Val Lys Ala Ile Trp Glu Ala Arg Cys Ser Glu Trp Ala Glu
115 120 125
Thr Glu Arg Phe Tyr Pro Phe Leu Glu Thr Gln Val Ser Pro Pro Glu
130 135 140
Ile Ala Leu Thr Thr Gly Glu Lys Ser Ile Ser Ile Ala Leu Thr Ala
145 150 155 160
Pro Glu Lys Trp Lys Arg Asn Pro Gln Asp His Thr Val Ser Met Gln
165 170 175
Gln Ile Tyr Pro Asn Leu Lys Tyr Asn Val Ser Val Tyr Asn Thr Lys
180 185 190
Ser Arg Arg Thr Trp Ser Gln Cys Val Thr Asn Ser Thr Leu Val Leu
195 200 205
Ser Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Leu
210 215 220
Val Pro Gly Pro Pro Arg Leu Pro Met Pro Ser Gln Lys Gln Cys Ile
225 230 235 240
Ser Thr Leu Glu Val Gln Thr Ser Ala Trp Lys Ala Lys Val Ile Phe
245 250 255
Trp Tyr Val Phe Leu Thr Ser Val Ile Val Phe Leu Phe Ser Ala Ile
260 265 270
Gly Tyr Leu Val Tyr Arg Tyr Ile His Val Gly Lys Glu Lys His Pro
275 280 285
Ala Asn Leu Val Leu Ile Tyr Arg Asn Glu Ile Gly Thr Arg Val Phe
290 295 300
Glu Pro Thr Glu Thr Ile Thr Leu Asn Phe Ile Thr Phe Ser Met Leu
305 310 315 320
Asp Asp Thr Lys Ile Ser Pro Lys Asp Met Asn Leu Leu Asp Lys Ser
325 330 335
Ser Asp Asp Ile Ser Val Asn Asp Pro Glu His Asn Glu Ala Trp Glu
340 345 350
Pro His Trp Glu Glu Val Glu Gly Gln His Leu Gly Cys Ser Ser His
355 360 365
Leu Met Asp Ala Val Cys Gly Ala Glu Gln Arg Asp Gly Asp Thr Ser
370 375 380

Leu Thr Gln His Gly Trp Leu Asn Ser Thr Ile Pro Thr Gly Glu Thr
385 390 395 400
Asp Thr Glu Pro Gln Tyr Lys Val Leu Ser Asp Phe Tyr Gly Glu Gly
405 410 415
Glu Ile Gln Leu Ser Cys Glu Pro Glu Glu Ala Ala Arg Thr Glu Lys
420 425 430
Ile Ser Glu Pro Leu Val Thr Ser Ala Asn Leu Asp Pro Gln Leu Glu
435 440 445
Asp Leu His His Leu Gly Gln Glu His Thr Val Ser Glu Asp Gly Pro
450 455 460
Glu Glu Glu Thr Ser Ile Thr Val Val Asp Trp Asp Pro Gln Thr Gly
465 470 475 480
Arg Leu Cys Ile Pro Ser Leu Pro Ile Phe Gly Arg Asp Pro Glu Asn
485 490 495
Tyr Gly His Tyr Glu Arg Asp Gln Leu Leu Glu Gly Gly Leu Leu Ser
500 505 510
Arg Leu Tyr Glu Asn Gln Ala Pro Asp Lys Pro Glu Lys Glu Asn Glu
515 520 525
Asn Cys Leu Thr Arg Phe Met Glu Glu Trp Gly Leu His Val Gln Met
530 535 540
Glu Ser
545

<210> 38
<211> 217
<212> PRT
<213> Mus musculus

<400> 38
Val Pro Cys Val Phe Cys Gly Leu Pro Lys Pro Thr Asn Ile Thr Phe
1 5 10 15
Leu Ser Ile Asn Met Lys Asn Val Leu His Trp Asn Pro Pro Glu Ser
20 25 30
Leu His Gly Val Glu Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
35 40 45
Gln Lys Lys Trp Leu Asn Ala Ser Lys Cys Gly Ser Ile Asn Arg Thr
50 55 60
Tyr Cys Asp Leu Ser Val Glu Thr Ser Asp Tyr Glu His Gln Phe Tyr
65 70 75 80
Ala Lys Val Lys Ala Ile Trp Glu Ala Arg Cys Ser Glu Trp Ala Glu
85 90 95
Thr Glu Arg Phe Tyr Pro Phe Leu Glu Thr Gln Val Ser Pro Pro Glu
100 105 110

Ile Ala Leu Thr Thr Gly Glu Lys Ser Ile Ser Ile Ala Leu Thr Ala
115 120 125
Pro Glu Lys Trp Lys Arg Asn Pro Gln Asp His Thr Val Ser Met Gln
130 135 140
Gln Ile Tyr Pro Asn Leu Lys Tyr Asn Val Ser Val Tyr Asn Thr Lys
145 150 155 160
Ser Arg Arg Thr Trp Ser Gln Cys Val Thr Asn Ser Thr Leu Val Leu
165 170 175
Ser Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Leu
180 185 190
Val Pro Gly Pro Pro Arg Leu Pro Met Pro Ser Gln Lys Gln Cys Ile
195 200 205
Ser Thr Leu Glu Val Gln Thr Ser Ala
210 215

<210> 39
<211> 514
<212> PRT
<213> Mus musculus

<400> 39
Val Pro Cys Val Phe Cys Gly Leu Pro Lys Pro Thr Asn Ile Thr Phe
1 5 10 15
Leu Ser Ile Asn Met Lys Asn Val Leu His Trp Asn Pro Pro Glu Ser
20 25 30
Leu His Gly Val Glu Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
35 40 45
Gln Lys Lys Trp Leu Asn Ala Ser Lys Cys Gly Ser Ile Asn Arg Thr
50 55 60
Tyr Cys Asp Leu Ser Val Glu Thr Ser Asp Tyr Glu His Gln Phe Tyr
65 70 75 80
Ala Lys Val Lys Ala Ile Trp Glu Ala Arg Cys Ser Glu Trp Ala Glu
85 90 95
Thr Glu Arg Phe Tyr Pro Phe Leu Glu Thr Gln Val Ser Pro Pro Glu
100 105 110
Ile Ala Leu Thr Thr Gly Glu Lys Ser Ile Ser Ile Ala Leu Thr Ala
115 120 125
Pro Glu Lys Trp Lys Arg Asn Pro Gln Asp His Thr Val Ser Met Gln
130 135 140
Gln Ile Tyr Pro Asn Leu Lys Tyr Asn Val Ser Val Tyr Asn Thr Lys
145 150 155 160
Ser Arg Arg Thr Trp Ser Gln Cys Val Thr Asn Ser Thr Leu Val Leu
165 170 175

Ser Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Leu
180 185 190
Val Pro Gly Pro Pro Arg Leu Pro Met Pro Ser Gln Lys Gln Cys Ile
195 200 205
Ser Thr Leu Glu Val Gln Thr Ser Ala Trp Lys Ala Lys Val Ile Phe
210 215 220
Trp Tyr Val Phe Leu Thr Ser Val Ile Val Phe Leu Phe Ser Ala Ile
225 230 235 240
Gly Tyr Leu Val Tyr Arg Tyr Ile His Val Gly Lys Glu Lys His Pro
245 250 255
Ala Asn Leu Val Leu Ile Tyr Arg Asn Glu Ile Gly Thr Arg Val Phe
260 265 270
Glu Pro Thr Glu Thr Ile Thr Leu Asn Phe Ile Thr Phe Ser Met Leu
275 280 285
Asp Asp Thr Lys Ile Ser Pro Lys Asp Met Asn Leu Leu Asp Lys Ser
290 295 300
Ser Asp Asp Ile Ser Val Asn Asp Pro Glu His Asn Glu Ala Trp Glu
305 310 315 320
Pro His Trp Glu Glu Val Glu Gly Gln His Leu Gly Cys Ser Ser His
325 330 335
Leu Met Asp Ala Val Cys Gly Ala Glu Gln Arg Asp Gly Asp Thr Ser
340 345 350
Leu Thr Gln His Gly Trp Leu Asn Ser Thr Ile Pro Thr Gly Glu Thr
355 360 365
Asp Thr Glu Pro Gln Tyr Lys Val Leu Ser Asp Phe Tyr Gly Glu Gly
370 375 380
Glu Ile Gln Leu Ser Cys Glu Pro Glu Glu Ala Ala Arg Thr Glu Lys
385 390 395 400
Ile Ser Glu Pro Leu Val Thr Ser Ala Asn Leu Asp Pro Gln Leu Glu
405 410 415
Asp Leu His His Leu Gly Gln Glu His Thr Val Ser Glu Asp Gly Pro
420 425 430
Glu Glu Glu Thr Ser Ile Thr Val Val Asp Trp Asp Pro Gln Thr Gly
435 440 445
Arg Leu Cys Ile Pro Ser Leu Pro Ile Phe Gly Arg Asp Pro Glu Asn
450 455 460
Tyr Gly His Tyr Glu Arg Asp Gln Leu Leu Glu Gly Gly Leu Leu Ser
465 470 475 480
Arg Leu Tyr Glu Asn Gln Ala Pro Asp Lys Pro Glu Lys Glu Asn Glu
485 490 495
Asn Cys Leu Thr Arg Phe Met Glu Glu Trp Gly Leu His Val Gln Met
500 505 510
Glu Ser

<210> 40
<211> 18
<212> DNA
<213> Mus musculus

<400> 40
cgccgcgttc ccgagatg 18

<210> 41
<211> 24
<212> DNA
<213> Mus musculus

<400> 41
ggatgaggca gggctgacaa agtt 24

<210> 42
<211> 36
<212> DNA
<213> Homo sapiens

<400> 42
acttgtggaa ttcgctagca ccaagggccc atcggt 36

<210> 43
<211> 32
<212> DNA
<213> Homo sapiens

<400> 43
gcctagaacg cgttcattta cccggagaca gg 32

<210> 44
<211> 8
<212> DNA
<213> Homo sapiens

<400> 44
aattgaga 8

<210> 45
<211> 8

<212> DNA
<213> Homo sapiens

<400> 45
cgcgtctc 8

<210> 46
<211> 37
<212> DNA
<213> Homo sapiens

<400> 46
gtcacttgaa ttcggtaccg cctctgttgt gtgcctg 37

<210> 47
<211> 32
<212> DNA
<213> Homo sapiens

<400> 47
gacctgaacg cgtctaacac tctcccctgt tg 32

<210> 48
<211> 38
<212> DNA
<213> Homo sapiens

<400> 48
tcagtcggaa ttcgcagaag ccatgcgggc tcccggcc 38

<210> 49
<211> 35
<212> DNA
<213> Homo sapiens

<400> 49
ctgtgacgct agcctctgat gattgatctt tcaaa 35

<210> 50
<211> 43
<212> DNA
<213> Homo sapiens

<400> 50
gatgtctgaa ttcgcagaag ccatgcagac tttcacaatg gtt 43

<210> 51
<211> 86
<212> DNA
<213> Homo sapiens

<400> 51
aagacggtac cagatttcaa ctgctcatca gatggcggga agatgaagac agatggtgca 60
gccacagtgg cctctccttg cacctc 86

<210> 52
<211> 1720
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1713)

<400> 52
atg cgg gct ccc ggc cgc ccg gcc ctg cgg ccg ctg ctg ctg ttg ctc 48
Met Arg Ala Pro Gly Arg Pro Ala Leu Arg Pro Leu Leu Leu Leu Leu
1 5 10 15

ctg gcg gcg cct tgg gga cgg gca gtt ccc tgt gtc tct ggt ggt ttg 96
Leu Ala Ala Pro Trp Gly Arg Ala Val Pro Cys Val Ser Gly Gly Leu
20 25 30

cct aaa cct gca aac atc acc ttc tta tcc atc aac atg aag aat gtc 144
Pro Lys Pro Ala Asn Ile Thr Phe Leu Ser Ile Asn Met Lys Asn Val
35 40 45

cta caa tgg act cca cca gag ggt ctt caa gga gtt aaa gtt act tac 192
Leu Gln Trp Thr Pro Pro Glu Gly Leu Gln Gly Val Lys Val Thr Tyr
50 55 60

act gtg cag tat ttc ata tat ggg caa aag aaa tgg ctg aat aaa tca 240
Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys Ser
65 70 75 80

gaa tgc aga aat atc aat aga acc tac tgt gat ctt tct gct gaa act 288

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Glu Cys Arg Asn Ile Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr
                 85                  90                  95

tct gac tac gaa cac cag tat tat gcc aaa gtt aag gcc att tgg gga       336
Ser Asp Tyr Glu His Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly
            100                 105                 110

aca aag tgt tcc aaa tgg gct gaa agt gga cgg ttc tat cct ttt tta       384
Thr Lys Cys Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu
        115                 120                 125

gaa aca caa att ggc cca cca gag gtg gca ctg act aca gat gag aag       432
Glu Thr Gln Ile Gly Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys
    130                 135                 140

tcc att tct gtt gtc ctg aca gct cca gag aag tgg aag aga aat cca       480
Ser Ile Ser Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro
145                 150                 155                 160

gaa gac ctt cct gtt tcc atg caa caa ata tac tcc aat ctg aag tat       528
Glu Asp Leu Pro Val Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys Tyr
                165                 170                 175

aac gtg tct gtg ttg aat act aaa tca aac aga acg tgg tcc cag tgt       576
Asn Val Ser Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys
            180                 185                 190

gtg acc aac cac acg ctg gtg ctc acc tgg ctg gag ccg aac act ctt       624
Val Thr Asn His Thr Leu Val Leu Thr Trp Leu Glu Pro Asn Thr Leu
        195                 200                 205

tac tgc gta cac gtg gag tcc ttc gtc cca ggg ccc cct cgc cgt gct       672
Tyr Cys Val His Val Glu Ser Phe Val Pro Gly Pro Pro Arg Arg Ala
    210                 215                 220

cag cct tct gag aag cag tgt gcc agg act ttg aaa gat caa tca tca       720
Gln Pro Ser Glu Lys Gln Cys Ala Arg Thr Leu Lys Asp Gln Ser Ser
225                 230                 235                 240

gag gct agc acc aag ggc cca tcg gtc ttc ccc ctg gca ccc tcc tcc       768
Glu Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
                245                 250                 255
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aag agc acc tct ggg ggc aca gcg gcc ctg ggc tgc ctg gtc aag gac 816
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
260 265 270

tac ttc ccc gaa ccg gtg acg gtg tcg tgg aac tca ggc gcc ctg acc 864
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
275 280 285

agc ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctc tac 912
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
290 295 300

tcc ctc agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acc cag 960
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
305 310 315 320

acc tac atc tgc aac gtg aat cac aag ccc agc aac acc aag gtg gac 1008
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
325 330 335

aag aaa gtt gag ccc aaa tct tgt gac aaa act cac aca tgc cca ccg 1056
Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
340 345 350

tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc ccc 1104
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
355 360 365

cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct gag gtc aca 1152
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
370 375 380

tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc aac 1200
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
385 390 395 400

tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg 1248
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
405 410 415

gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc 1296
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
420 425 430

ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc tcc 1344
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
435 440 445

aac aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc aaa gcc aaa 1392
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
450 455 460

ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg gat 1440
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
465 470 475 480

gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc 1488
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
485 490 495

tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg gag 1536
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
500 505 510

aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc 1584
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
515 520 525

ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg cag cag ggg 1632
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
530 535 540

aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac tac 1680
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
545 550 555 560

acg cag aag agc ctc tcc ctg tct ccg ggt aaa tgacgcg 1720
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
565 570

<210> 53
<211> 571
<212> PRT
<213> Homo sapiens

<400> 53

Met Arg Ala Pro Gly Arg Pro Ala Leu Arg Pro Leu Leu Leu Leu Leu
1 5 10 15
Leu Ala Ala Pro Trp Gly Arg Ala Val Pro Cys Val Ser Gly Gly Leu
20 25 30
Pro Lys Pro Ala Asn Ile Thr Phe Leu Ser Ile Asn Met Lys Asn Val
35 40 45
Leu Gln Trp Thr Pro Pro Glu Gly Leu Gln Gly Val Lys Val Thr Tyr
50 55 60
Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys Ser
65 70 75 80
Glu Cys Arg Asn Ile Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr
85 90 95
Ser Asp Tyr Glu His Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly
100 105 110
Thr Lys Cys Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu
115 120 125
Glu Thr Gln Ile Gly Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys
130 135 140
Ser Ile Ser Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro
145 150 155 160
Glu Asp Leu Pro Val Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys Tyr
165 170 175
Asn Val Ser Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys
180 185 190
Val Thr Asn His Thr Leu Val Leu Thr Trp Leu Glu Pro Asn Thr Leu
195 200 205
Tyr Cys Val His Val Glu Ser Phe Val Pro Gly Pro Pro Arg Arg Ala
210 215 220
Gln Pro Ser Glu Lys Gln Cys Ala Arg Thr Leu Lys Asp Gln Ser Ser
225 230 235 240
Glu Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
245 250 255
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
260 265 270
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
275 280 285
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
290 295 300
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
305 310 315 320
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
325 330 335

340 345 350
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
355 360 365
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
370 375 380
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
385 390 395 400
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
405 410 415
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
420 425 430
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
435 440 445
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
450 455 460
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
465 470 475 480
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
485 490 495
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
500 505 510
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
515 520 525
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
530 535 540
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
545 550 555 560
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
565 570

<210> 54
<211> 547
<212> PRT
<213> Homo sapiens

<400> 54
Val Pro Cys Val Ser Gly Gly Leu Pro Lys Pro Ala Asn Ile Thr Phe
1 5 10 15
Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp Thr Pro Pro Glu Gly
20 25 30
Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
35 40 45

Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr
50 55 60

Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr
65 70 75 80

Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu
85 90 95

Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu
100 105 110

Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala
115 120 125

Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln
130 135 140

Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys
145 150 155 160

Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu
165 170 175

Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe
180 185 190

Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala
195 200 205

Arg Thr Leu Lys Asp Gln Ser Ser Glu Ala Ser Thr Lys Gly Pro Ser
210 215 220

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
225 230 235 240

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
245 250 255

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
260 265 270

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
275 280 285

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
290 295 300

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
305 310 315 320

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
325 330 335

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
340 345 350

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
355 360 365

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
370 375 380

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
385 390 395 400
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
405 410 415
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
420 425 430
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
435 440 445
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
450 455 460
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
465 470 475 480
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
485 490 495
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
500 505 510
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
515 520 525
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
530 535 540
Pro Gly Lys
545

<210> 55
<211> 217
<212> PRT
<213> Homo sapiens

<400> 55
Val Pro Cys Val Ser Gly Gly Leu Pro Lys Pro Ala Asn Ile Thr Phe
1 5 10 15
Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp Thr Pro Pro Glu Gly
20 25 30
Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
35 40 45
Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr
50 55 60
Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr
65 70 75 80
Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu
85 90 95
Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu
100 105 110

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Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala
        115                 120                 125
Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln
    130                 135                 140
Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys
145                 150                 155                 160
Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu
                165                 170                 175
Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe
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Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala
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atg tgg ttt ttc tac gca ttg att cca tgt ttg ctc aca gat gaa gtg       96
Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
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gcc att ctg cct gcc cct cag aac ctc tct gta ctc tca acc aac atg      144
Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
        35                  40                  45

aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga gaa aca gtg      192
Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
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tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg tac acg agc      240
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His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
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Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
            100                 105                 110

gtc agg gcc aca ttg ggc tca cag acc tca gcc tgg agc atc ctg aag      384
Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
        115                 120                 125

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His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
    130                 135                 140

atc acc aaa gat ggc ttc cac ctg gtt att gag ctg gag gac ctg ggg      480
Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
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ccc cag ttt gag ttc ctt gtg gcc tac tgg agg agg gag cct ggt gcc      528
Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu Pro Gly Ala
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gag gaa cat gtc aaa atg gtg agg agt ggg ggt att cca gtg cac cta      576
Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
            180                 185                 190

gaa acc atg gag cca ggg gct gca tac tgt gtg aag gcc cag aca ttc      624
Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
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gtg aag gcc att ggg agg tac agc gcc ttc agc cag aca gaa tgt gtg      672
Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
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Glu Val Gln Gly Glu Ala Thr Val Ala Ala Pro Ser Val Phe Ile Phe
225                 230                 235                 240
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ctg ctg aat aac ttc tat ccc aga gag gcc aaa gta cag tgg aag gtg 816
Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
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gat aac gcc ctc caa tcg ggt aac tcc cag gag agt gtc aca gag cag 864
Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
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gac agc aag gac agc acc tac agc ctc agc agc acc ctg acg ctg agc 912
Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
290 295 300

aaa gca gac tac gag aaa cac aaa gtc tac gcc tgc gaa gtc acc cat 960
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cag ggc ctg agc tcg ccc gtc aca aag agc ttc aac agg gga gag tgt 1008
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35 40 45
Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
50 55 60
Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
65 70 75 80

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Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
100 105 110
Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
115 120 125
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130 135 140
Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
145 150 155 160
Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu Pro Gly Ala
165 170 175
Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
180 185 190
Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
195 200 205
Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
210 215 220
Glu Val Gln Gly Glu Ala Thr Val Ala Ala Pro Ser Val Phe Ile Phe
225 230 235 240
Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
245 250 255
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260 265 270
Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
275 280 285
Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
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Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
50 55 60
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
65 70 75 80
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
85 90 95
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
100 105 110
Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu
115 120 125
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu
130 135 140
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
145 150 155 160
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
165 170 175
Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
180 185 190
Glu Cys Val Glu Val Gln Gly Glu Ala Thr Val Ala Ala Pro Ser Val
195 200 205
Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
210 215 220
Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
225 230 235 240
Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
245 250 255
Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
260 265 270
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35 40 45
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
50 55 60
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
65 70 75 80
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
85 90 95
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
100 105 110
Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu
115 120 125
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu
130 135 140
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
145 150 155 160
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
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180 185 190
Glu Cys Val Glu Val Gln Gly Glu Ala
195 200

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20 25 30
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35 40 45
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
50 55 60
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
65 70 75 80

Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
85 90 95
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
100 105 110
Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu
115 120 125
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu
130 135 140
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
145 150 155 160
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
165 170 175
Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
180 185 190
Glu Cys Val Glu Val Gln Gly Glu Ala Gly Gly Gly Gly Ser Gly Gly
195 200 205
Gly Gly Ser Gly Gly Gly Gly Ser Arg Thr Val Ala Ala Pro Ser Val
210 215 220
Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
225 230 235 240
Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
245 250 255
Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
260 265 270
Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
275 280 285
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305 310 315 320
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35 40 45
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
50 55 60
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
65 70 75 80
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
85 90 95
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
100 105 110
Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu
115 120 125
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu
130 135 140
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
145 150 155 160
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
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35 40 45
Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr
50 55 60
Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr
65 70 75 80
Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu
85 90 95
Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu
100 105 110

Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala
115 120 125
Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln
130 135 140
Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys
145 150 155 160
Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu
165 170 175
Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe
180 185 190
Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala
195 200 205
Arg Thr Leu Lys Asp Gln Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
210 215 220
Gly Gly Gly Gly Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
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Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
245 250 255
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260 265 270
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
275 280 285
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
290 295 300
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305 310 315 320
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
325 330 335
Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val
340 345 350
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
355 360 365
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
370 375 380
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
385 390 395 400
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
405 410 415
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
420 425 430
Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile
435 440 445

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
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Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
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Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
485 490 495
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35 40 45
Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr
50 55 60
Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr
65 70 75 80
Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu
85 90 95
Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu
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115 120 125
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130 135 140
Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys
145 150 155 160
Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu
165 170 175

Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe
180 185 190
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Tyr Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys
35 40 45
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50 55 60
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65 70 75 80
Gly Thr Lys Cys Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe
85 90 95
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100 105 110
Lys Ser Ile Ser Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn
115 120 125
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130 135 140
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145 150 155 160

Cys Val Thr Asn His Thr Leu Val Leu Thr Trp Leu Glu Pro Asn Thr
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Val Ser Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys Val
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Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys His Pro
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Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly Pro Gln
115 120 125
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His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu Glu Thr
145 150 155 160
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Gln Gly Glu Ala
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85 90 95

Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
100 105 110
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Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
145 150 155 160
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
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Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro
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65 70 75 80
Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys His Pro
85 90 95
Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu Ile Pro
100 105 110
Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly Pro Gln
115 120 125
Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro Gly Ala Glu Glu
130 135 140
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145 150 155 160
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85 90 95
Ser Gly Gly Ile Pro Val His Leu Glu Thr Met Glu Pro Gly Ala Ala
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35 40 45

Ile Leu Thr Arg Pro Gly Met Glu Ile Pro Lys His Gly Phe His Leu
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Val Ile Glu Leu Glu Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala
65 70 75 80
Tyr Trp Thr Arg Glu Pro Gly Ala Glu Glu His Val Lys Met Val Arg
85 90 95
Ser Gly Gly Ile Pro Val His Leu Glu Thr Met Glu Pro Gly Ala Ala
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130 135

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<400> 72
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INTERNATIONAL SEARCH REPORT

Int   onal Application No
PCT/US 00/35305

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/24 C07K16/28 C07K14/54 A61K39/395 C07K19/00
A61P17/06 A61P11/06 //C07K14/715

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 27103 A (ZYMOGENETICS INC) 3 June 1999 (1999-06-03) abstract page 2, line 10-36 page 4, line 13-17 page 5, line 5-17 page 19, line 11-33 page 37, line 11-33 page 41, line 19-24	1,2,7,8
Y	page 43, line 1-26	3-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2001	11.05.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Montrone, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 99 03982 A (FLORENCE KIMBERLY A ;HUMAN GENOME SCIENCES INC (US); DUAN ROXANNE) 28 January 1999 (1999-01-28) abstract page 2, line 34 -page 3, line 11 page 5, line 11-39 page 6, line 38 -page 7, line 2 page 35, line 7 -page 36, line 39 page 39, line 17 -page 41, line 21 page 45, line 19-31 page 46, line 20-25 ---	1,2 3-6
X Y	US 5 945 511 A (KHO CHOON J ET AL) 31 August 1999 (1999-08-31) abstract column 1, line 25-32 column 4, line 14-28 column 5, line 13-40 column 6, line 49-51 column 15, line 66 -column 16, line 28 column 17, line 1-51 column 18, line 18-21 ---	1,2 3-6
Y	MCKINNON M ET AL: "STRATEGIES FOR THE DISCOVERY OF CYTOKINE RECEPTOR ANTAGONISTS" DRUG NEWS AND PERSPECTIVES,XX,XX, vol. 9, 1996, pages 389-398, XP000882849 ISSN: 0214-0934 abstract page 391, column 1, paragraph 2 -column 3, paragraph 1; figure 1 ---	1-6
Y	MOHLER K M ET AL: "IMMUNOTHERAPEUTIC POTENTIAL OF SOLUBLE SYTOKINE RECEPTORS IN INFLAMMATORY DISEASE" FASEB JOURNAL,US,FED. OF AMERICAN SOC. FOR EXPERIMENTAL BIOLOGY, BETHESDA, MD, vol. 6, no. 4, 26 February 1992 (1992-02-26), page A1123 XP002015786 ISSN: 0892-6638 abstract --- -/--	1-6

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 42189 A (MURPHY MARIANNE ;FLORENCE KIMBERLY (US); HUMAN GENOME SCIENCES INC) 20 July 2000 (2000-07-20) page 3, line 4-17 page 5, line 27 -page 6, line 31 page 7, line 6-36 page 8, line 1-3 page 9, line 8-12 page 30, line 32-37 page 51, line 19 -page 53, line 26 page 55, line 9-14 page 57, line 9,10 page 62, line 23 -page 64, line 30 page 115, line 5 -page 116, line 25 -----	1,2,9,10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/35305

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 to 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int( )nal Application No
PCT/US 00/35305

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9927103 A	03-06-1999	AU 1607799 A	15-06-1999
		BR 9814904 A	03-10-2000
		CN 1282372 T	31-01-2001
		EP 1032671 A	06-09-2000
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WO 9903982 A	28-01-1999	AU 8404598 A	10-02-1999
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		EP 1009825 A	21-06-2000
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WO 0042189 A	20-07-2000	AU 2965600 A	01-08-2000